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Nathana Jamille Mezzomo

EFEITOS DO TIPO ANSIOLÍTICO E ANTIESTRESSE DA TAURINA EM PEIXE-ZEBRA (*Danio rerio*)

Santa Maria, RS
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Efeitos do tipo ansiolítico e antiestresse da taurina em peixe-zebra (*Danio rerio*)

Tese apresentada ao curso de Farmacologia, da Universidade Federal de Santa Maria (UFSM, RS) como requisito parcial para obtenção do título de Doutora em Farmacologia.

Orientador: Prof. Dr. Leonardo José Gil Barcellos
Co-orientador: Prof. Dr. Denis Broock Rosemberg

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A autora

“ A ciência moderna ainda não produziu um medicamento tranquilizador tão eficaz como o são umas poucas palavras boas. ”

Sigmund Freud

RESUMO

EFEITOS DO TIPO ANSIOLÍTICO E ANTIESTRESSE DA TAURINA EM PEIXE-ZEBRA (*Danio rerio*)

AUTORA: Nathana Jamille Mezzomo
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Os transtornos mentais são um grande desafio à saúde global, consideradas pandemias do século XXI. Cerca de um terço da incapacidade mundial é causada por problemas relacionados à saúde mental. Frente a isso, a Organização Mundial da Saúde desenvolveu um plano de ação, que busca novas estratégias de promoção e prevenção em saúde mental, e o fortalecimento das pesquisas na área. Portanto, os estudos que visam desvendar novas terapias na área de saúde mental tornam-se atraentes. A taurina tem sido estudada como terapia adjuvante em transtornos do sistema nervoso central (SNC), devido ao potencial de prevenção à excitotoxicidade do glutamato, regulação do cálcio, dos processos inflamatórios e estresse oxidativo. No presente estudo, buscamos melhor compreender as ações da taurina como tratamento dos transtornos mentais em humanos através do peixe-zebra (*Danio rerio*) como organismo modelo. Em uma revisão sistemática, descrevemos as suas principais contribuições e limitações como organismo modelo, avaliando os efeitos centrais da taurina em doenças neuropsiquiátricas. Ao fim, concluímos que o peixe-zebra é um organismo modelo com grande potencial para a avaliação dos efeitos neuroprotetores da taurina nessas doenças. Posteriormente, investigamos os efeitos de três concentrações de taurina (42, 150, 400 mg/L) em modelos comportamentais de estresse e ansiedade em peixe-zebra. Descobrimos que a taurina modula as respostas comportamentais e neuroendócrinas nessa espécie em diferentes contextos. No primeiro experimento, os peixes foram testados no teste do tanque novo e claro-escuro após o tratamento com taurina. Não observamos diferença comportamental no tanque novo, apenas no claro-escuro. Todas as concentrações de taurina evitaram o comportamento do tipo ansiedade (escotaxia) nos peixes, permitindo que passassem mais tempo na área clara, indicando atividade ansiolítica. No segundo experimento, os peixes foram desafiados a um estressor agudo mecânico (perseguição com rede) ou químico (exposição à substância de alarme de coespecífico; CAS) nos mesmos testes comportamentais anteriores. Todas concentrações de taurina evitaram comportamentos relacionados ao estresse desencadeados por CAS. A menor concentração de taurina também preveniu a carbonilação de proteínas ocasionada por perseguição com rede, sugerindo uma possível atividade antioxidante. No entanto, a maior concentração estimulou excessivamente tanto parâmetros oxidativos quando antioxidantes desencadeados pelos dois estressores. A maior concentração também inibiu a liberação de cortisol em resposta ao CAS, indicando ação antiestresse. Apesar dos fenótipos apresentados aqui representarem respostas complexas de interações multifacetadas de vários sistemas de neurotransmissores, acreditamos que a taurina possa exercer ação terapêutica em transtornos mentais relacionados ao estresse.

Palavras-chave: Aminoácido. Transtornos Mentais. Sistema Nervoso Central. Cortisol.

ABSTRACT

ANXIOLYTIC AND ANTI-STRESS EFFECTS OF TAURINE IN ZEBRAFISH (*Danio rerio*)

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ADVISOR: Dr. Leonardo José Gil Barcellos
CO-ADVISOR: Dr. Denis Broock Rosemberg

Mental disorders are a major challenge to global health, considered 21st century pandemics. About a third of the world's disability is caused by mental health problems. Faced with this situation, World Health Organization developed an action plan, which searches new strategies for promotion and prevention in mental health, and strengthening research in the area. Therefore, studies aimed at discovering new therapies in the area of mental health become attractive. Taurine has been studied as an adjuvant therapy in disorders of the central nervous system (CNS), due to the potential to prevent the glutamate excitotoxicity, calcium regulation, inflammatory processes and oxidative stress. Herein, we looking for to better understand the actions of taurine as a treatment for mental disorders in humans through zebrafish (*Danio rerio*) as a model organism. In a systematic review, we describe its main contributions and limitations as a model organism, assessing the central effects of taurine in neuropsychiatric diseases. Finally, we conclude that zebrafish is a model organism with great potential for assessing the neuroprotective effects of taurine in these diseases. Then, we investigated the effects of three concentrations of taurine (42, 150, 400 mg / L) on behavioral models of stress and anxiety in zebrafish. We found that taurine modulates the behavioral and neuroendocrine responses in this species in different contexts. In the first experiment, the fish were tested in the novel tank and light-dark test after treatment with taurine. We did not observe any behavioral difference in the novel tank, only in the light-dark test. All concentrations of taurine prevented the anxiety-like behavior (scotaxis) in fish, allowing them to spend more time in the light area, indicating anxiolytic activity. In the second experiment, the fish were challenged with an acute mechanical stressor (net chasing) or chemical stressor (coespecific alarm substance; CAS) in the same previous behavioral tests. All concentrations of taurine prevented stress-related behaviors triggered by CAS. The lower concentration of taurine also prevented the protein carbonylation caused by chasing with a net, suggesting e possible antioxidant activity. However, the higher concentration stimulated excessively both oxidative parameters and antioxidants triggered by the two stressors. The higher taurine concentration also inhibited the release of cortisol in response to CAS, indicating a possible anti-stress action. Although the phenotypes presented here represent a complex response to multifaceted interactions of various neurotransmitter systems, we believe that taurine can exert a therapeutic action on stress-related mental disorders.

Keywords: Amino acid. Mental disorders. Central Nervous System. Cortisol.

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LISTA DE SIGLAS E ABREVIATURAS

ACTH	Adrenocorticotropic hormone; originalmente derivada do inglês
Ca^{2+}	Íon cálcio
CAS	Conspecific alarm substance; originalmente derivada do inglês
CAT	Catalase
CDO	Cysteine dioxygenase; originalmente derivada do inglês
CRH	Corticotropin-releasing hormone; originalmente derivada do inglês
CSAD	Cysteine sulfinic acid decarboxylase; originalmente derivada do inglês
CO_2	Dióxido de carbono
$GABA_A$	Receptor ácido γ-aminobutírico, tipo A
GSH	Glutationa em sua forma reduzida
HPA	Hipotálamo-pituitária-adrenal, eixo
HPI	Hipotálamo-pituitária-inter-renal, eixo
IUPAC	International Union of Pure and Applied Chemistry
IHME	Institute for Health Metrics and Evaluation
ISRS	Inibidores seletivos da recaptação da serotonina, classe de antidepressivos
MK-801	Dizocilpine; originalmente derivada do inglês
Na^+	Íon sódio
NMDA	Receptor N-metil-D-aspartato
PAT1	Proton-coupled amino acid transporter 1; originalmente derivada do inglês
PC	Phosphatidylcholine; originalmente derivada do inglês
PE	Phosphatidylethanolamine; originalmente derivada do inglês
PTZ	Pentilenotetrazol
PKC	Protein kinase C; originalmente derivada do inglês
PKA	Protein kinase A; originalmente derivada do inglês
SNC	Sistema nervoso central
SOD	Superóxido dismutase
TauT	Taurine transporter; originalmente derivada do inglês
VRAC	Volume-regulated anion channel; originalmente derivada do inglês
VSOAC	Volume-stimulated organic osmolyte; originalmente derivada do inglês
WHO	World Health Organization

SUMÁRIO

1 INTRODUÇÃO

A saúde mental é o estado de bem-estar, no qual o indivíduo reconhece a sua própria capacidade, pode lidar com estresses corriqueiros da vida, capaz de produzir e contribuir socialmente (WHO, 2005). No entanto, quando esse estado é afetado negativamente, há grande risco do desenvolvimento de transtornos mentais.

Os transtornos mentais são um grande desafio à saúde global, consideradas pandemias do século XXI. Elas representam cerca de um terço da incapacidade mundial causada por problemas de saúde em adultos, resultando em inúmeras adversidades pessoais e socioeconômicas (LAKE e TURNER, 2017). Em resposta a isso, a Organização Mundial da Saúde publicou o "Plano de Ação em Saúde Mental 2013-2020" (WHO, 2013), que busca fortalecer lideranças; fornecer serviços integrados e responsivos; implementar estratégias de promoção e prevenção; e reforçar as evidências científicas em saúde mental. A partir disso, o estudo de moléculas neuroprotetoras que fortaleçam as investigações na área da neurociência tornam-se interessantes no campo translacional.

A taurina é conhecida como um neurotransmissor inibitório, por ser uma substância cerebral endógena com propriedades neuromodulatórias (WU e PRENTICE, 2010; CHAN et al., 2014). Essa molécula tem sido estudada como terapia adjuvante para diversas disfunções do sistema nervoso central (SNC) devido a pluralidade de suas funções, incluindo prevenção à excitotoxicidade do glutamato, regulação do cálcio, dos processos inflamatórios e estresse oxidativo (WU et al., 2005; WU e PRENTICE, 2010; LERDWEERAPHON et al., 2013; CHAN et al., 2014; MENZIE et al., 2014). Portanto, os estudos que visam desvendar as vias moleculares subjacentes às respostas fisiológicas da taurina, tornam-se atraentes utilizando diferentes modelos experimentais.

Deste modo, o objetivo principal desse trabalho baseia-se em elucidar os potenciais efeitos benéficos da taurina sobre as respostas comportamentais e neuroendócrinas utilizando o peixe-zebra como organismo modelo. Esse estudo apresenta três hipóteses principais: a primeira refere-se ao potencial uso do peixe-zebra como organismo modelo na avaliação dos efeitos centrais da taurina em transtornos do SNC; e as outras duas fazem referência a capacidade da taurina em modular as respostas de ansiedade, e de estresse em peixe-zebra. Por fim, a partir dessas análises buscou-se obter um melhor entendimento das ações da taurina como tratamento dos transtornos mentais.

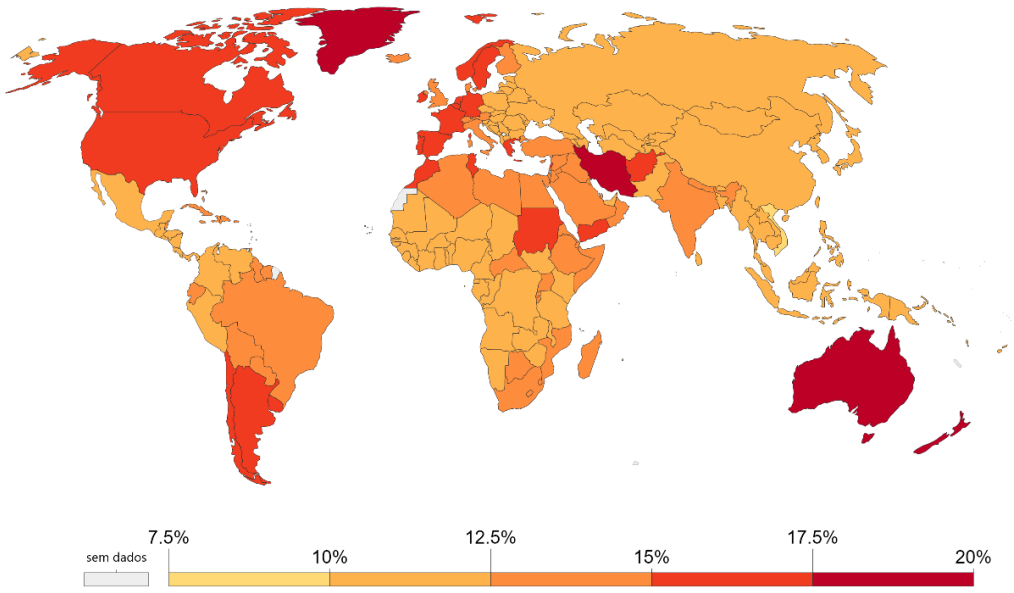
2 REVISÃO BIBLIOGRÁFICA

2.1 TRANSTORNOS DE SAÚDE MENTAL

A prevalência de transtornos de saúde mental e doenças associadas descritas no estudo ‘Global Burden of Disease’ conduzido pelo ‘Institute for Health Metrics and Evaluation’ (IHME, 2017), foi estimada em torno de uma para cada dez pessoas no mundo (10,7%) no ano de 2017 (Figura 1). O Brasil é o país que tem o maior número de pessoas ansiosas: 18,6 milhões de brasileiros (9,3% da população) convivem com transtorno de ansiedade (Figura 2), conforme dados da Organização Mundial da Saúde (WHO, 2017).

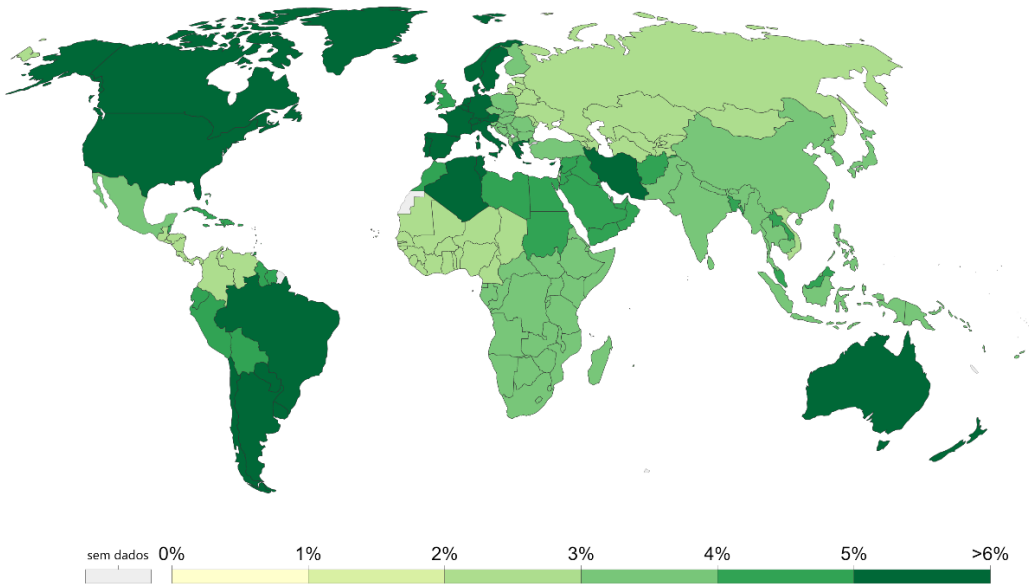
Os transtornos mentais com maior prevalência na população mundial dividem-se em dois diagnósticos principais: transtornos depressivos e transtornos de ansiedade. Esses transtornos têm grande impacto sobre o humor e os sentimentos, com sintomas variando em termos de gravidade (de leve a grave) e duração (de meses a anos). Essas condições de saúde são diagnosticáveis e diferem-se dos sentimentos comuns de tristeza, estresse ou medo cotidianamente vivenciados por qualquer pessoa (WHO, 2017).

Figura 1 - Prevalência mundial dos transtornos de saúde mental no ano de 2017



Fonte: imagem adaptada de ‘Institute for Health Metrics and Evaluation (IHME)’, 2017.

Figura 2 - Prevalência mundial dos transtornos de ansiedade no ano de 2017



Fonte: imagem adaptada de 'Institute for Health Metrics and Evaluation (IHME)', 2017.

Diversas variáveis favorecem o desenvolvimento de transtornos mentais, tais como: estresse, genética, nutrição, infecções perinatais e exposição a riscos ambientais. Entretanto, os atributos individuais (como a capacidade de gerenciar pensamentos, emoções, comportamentos e interações), e os fatores sociais, culturais, econômicos, políticos e ambientais (como as políticas nacionais, proteção social, padrões de vida, condições de trabalho e apoio comunitário) também são determinantes para saúde mental (WHO, 2017).

Os transtornos mentais representam maior custo econômico quando comparado às doenças somáticas crônicas, por exemplo. Além de custos associados ao diagnóstico e tratamento no sistema de saúde, existe o custo relacionado à perda de renda devido a mortalidade, perda de produção, incapacidade ou aposentadoria precoce. Avalia-se que entre os anos de 2011 e 2030, o prejuízo cumulativo da produção econômica seja em torno de US$ 16,3 trilhões no mundo, sendo comparável às doenças cardiovasculares e superior à do câncer, doenças respiratórias crônicas e diabetes (TRAUTMANN et al., 2016).

Muitos pacientes com esses transtornos não procuram atendimento médico e psicoterapêutico. Além disso, existe uma lacuna entre a necessidade de tratamento e sua disponibilidade no sistema de saúde (CHISHOLM et al., 2016; TRAUTMANN et al., 2016). Em vista disso, a promoção da saúde mental e a pesquisa de novas estratégias farmacológicas são fundamentais na busca da resolução dessa problemática de saúde pública.

2.1.1 Estresse Emocional

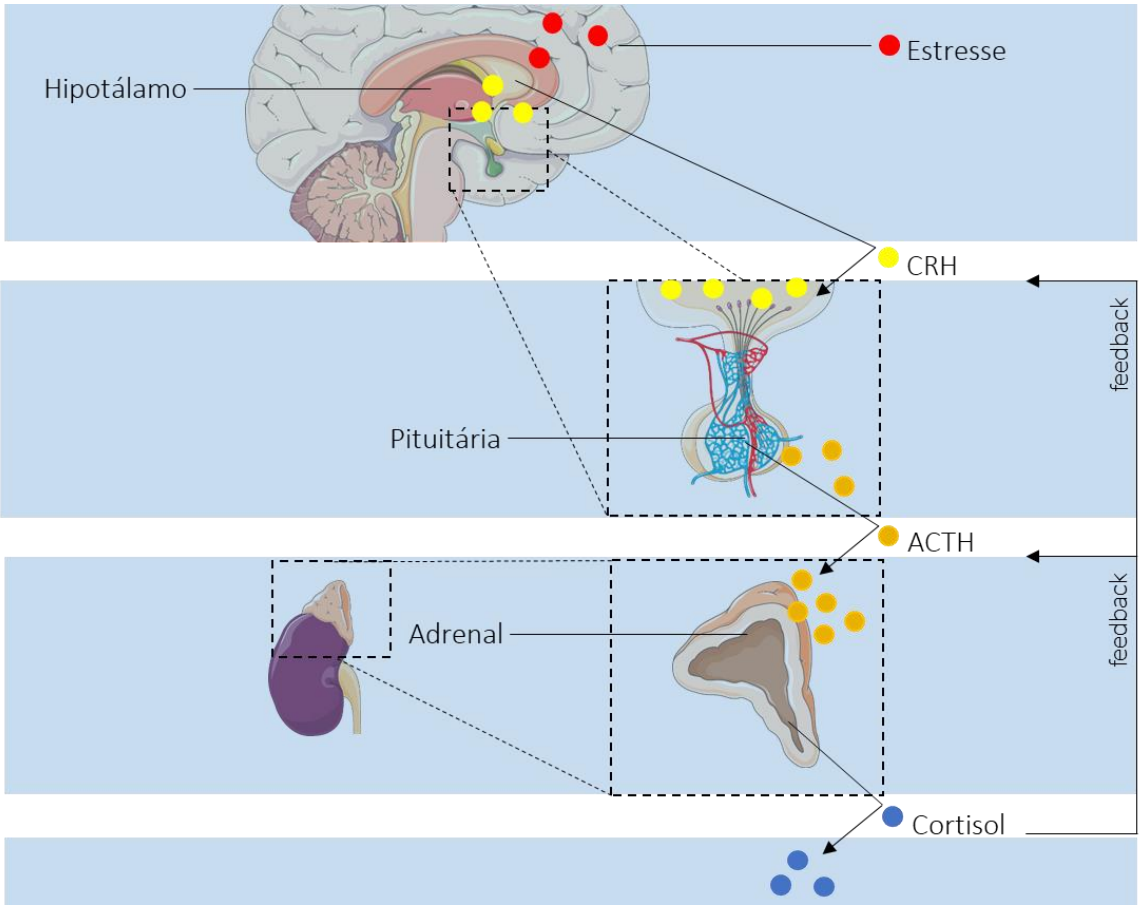
Apesar de não ser classificado como um transtorno psiquiátrico, o sofrimento grave (também denominado ‘distress’), é um dos critérios diagnósticos para transtornos mentais (TRAUTMANN et al., 2016). O início, os fatores envolvidos, e a gravidade dos transtornos mentais são complexos, e raramente podem ser atribuídos a um único determinante. Por exemplo, o estresse no trabalho, a imaturidade emocional e dificuldade na comunicação são fatores de risco de circunstância social e de atributos individuais. Por outro lado, a capacidade de resolver problemas e gerenciar o estresse são fatores protetivos para o bom desenvolvimento da saúde mental (WHO, 2012). Portanto, o estresse emocional pode ser um fator desencadeador, ou ainda um fator agravante nos transtornos mentais.

O estresse é a palavra usada para descrever experiências que provocam reações emocionais e fisiológicas em um determinado organismo. O "estresse bom", no jargão popular, geralmente se refere às experiências de duração limitada, que se pode dominar, resultando em uma sensação de realização. Enquanto o "estresse ruim" ou ‘distress’, refere-se a experiências onde há falha do controle e domínio. Quando tais experiências são severamente prolongadas ou recorrentes, ocasionam esgotamento emocional e físico, suscetíveis ao desenvolvimento de transtornos mentais (MCEWEN, 2007).

A principal característica da resposta ao estresse é a ativação do eixo hipotálamo-pituitária-adrenal (HPA), que resulta na liberação de glicocorticoides, principalmente de cortisol (WALKER et al., 2008). Após um evento estressante, o hipotálamo libera o hormônio liberador da corticotrofina (CRH), que é transportado até a hipófise anterior, onde estimula a secreção e liberação do hormônio adrenocorticotrófico (ACTH), que por sua vez estimula a produção e liberação do cortisol pela glândula adrenal (Figura 3). Quando os níveis de cortisol estão aumentados, ocorre feedback negativo (efeito inibitório) à liberação hormonal em um ou mais pontos do eixo. Por fim, os glicocorticoides interagem com seus receptores em múltiplos tecidos-alvo do corpo promovendo diferentes efeitos fisiológicos (VILELA e JURUENA, 2014). Evidências demonstram que a função de receptores de glicocorticoides se encontra prejudicada na depressão maior, resultando em menor feedback negativo no eixo HPA, e secreção aumentada de CRH em várias regiões cerebrais. Além disso, os antidepressivos podem ter efeitos diretos nesses receptores, levando à sua hiperfunção e expressão aumentada (JURUENA et al., 2003; TOFOLI et al., 2011; VILELA e JURUENA, 2014).

A desregulação do eixo HPA também está associada a outros transtornos como transtornos de estresse pós-traumático e transtornos de ansiedade (HOLSBOER, 2000; NEWPORT e NEMEROFF, 2000; WALKER et al., 2013; MORENO-PERAL et al., 2014). Assim, o papel dos hormônios adrenocorticais no desencadeamento dos transtornos mentais tornou-se um foco significativo de pesquisa. A importância desta área de investigação é destacada pelos avanços da compreensão da sinalização neuro-hormonal, bem como da etiologia dos transtornos mentais (WALKER et al., 2008; WALKER et al., 2013).

Figura 3 - Funcionamento do eixo hipotálamo-pituitária-adrenal (HPA)



Fonte: autoria própria.

2.1.2 Transtornos de Ansiedade

Os transtornos de ansiedade abrangem um grupo de transtornos mentais caracterizados principalmente pelos sentimentos de ansiedade e de medo. Os transtornos desse grupo são classificados em: transtorno de ansiedade generalizada (TAG), transtorno do pânico, fobias, transtorno da ansiedade social, transtorno obsessivo-compulsivo (TOC) e transtorno de estresse pós-traumático (TEPT) (WHO, 2017). Eles surgem de uma combinação de traços vulneráveis de personalidade em um contexto de estressores e adversidades psicossociais (tais como a falta de apoio, as dificuldades, os relacionamentos disfuncionais, etc.). Tipicamente são desencadeados por eventos de alto nível de sofrimento, como a morte de um ente querido, manifestação de uma doença, acontecimento de um parto, ou um assédio moral no local de trabalho (WILKINS, 2019). Os indivíduos com transtornos de ansiedade frequentemente estão preocupados com acontecimentos futuros, apresentando dificuldade em vivenciar o momento (ROBICHAUD et al., 2019).

O critério de diagnóstico para cada tipo de transtorno de ansiedade é feito de forma singular. No entanto, segundo a Classificação Internacional de Doenças (CID-10), três sintomas são mais frequentes: a apreensão (preocupações com infortúnios futuros, sensação de nervosismo, dificuldade de concentração etc.); a tensão motora (inquietação, dores de cabeça tensionais, tremores, incapacidade de relaxar); e a hiperatividade autonômica (tontura, sudorese, taquicardia ou taquipneia, desconforto epigástrico, tontura, boca seca) (WHO, 1992). Os pacientes com transtorno de ansiedade apresentam outros problemas de saúde mental associados, dentre eles, os transtornos depressivos (comorbidade mais comum), e os transtornos adicionais ao próprio transtorno de ansiedade (transtorno de ansiedade social associado ao transtorno do pânico, por exemplo) (ROBICHAUD et al., 2019).

Apesar da sua apresentação sutil e insidiosa, os indivíduos acometidos com esse transtorno têm prejuízos significativos nos índices de qualidade de vida, além de inúmeras consequências como: a redução de oportunidades educacionais e ocupacionais, o comprometimento funcional, e o aumento de taxas de mortalidade em comparação àqueles indivíduos sem transtorno de ansiedade (JALNAPURKAR et al., 2018; WILKINS, 2019). Sabe-se que as mulheres são mais propensas que os homens a terem diagnóstico de algum transtorno de ansiedade durante a vida. Esse fato deve-se ao papel dos hormônios reprodutivos, e até mesmo diferenças anatômicas estruturais cerebrais responsáveis pelos

circuitos relacionados à ansiedade. Além disso, são relatadas diferenças na sintomatologia, no metabolismo e na resposta à farmacoterapia (JALNAPURKAR et al., 2018).

Apesar dos transtornos de ansiedade serem comuns e muitas vezes incapacitantes, eles são pouco reconhecidos e precariamente tratados na prática clínica. Ademais, estima-se que menos da metade das pessoas com transtornos de ansiedade busquem tratamento com um profissional na área da saúde (WILKINS, 2019). Os tratamentos considerados de primeira linha são: a terapia cognitivo-comportamental, e os antidepressivos da classe dos inibidores seletivos da recaptação da serotonina (ISRS; como paroxetina, citalopram, sertralina, fluoxetina e escitalopram) (JALNAPURKAR et al., 2018). Como alternativas ao uso de ISRS para pacientes com transtornos de ansiedade resistentes ou intolerantes ao tratamento, pode-se incluir: a buspirona, os antipsicóticos de segunda geração (quetiapina), e o valproato (ABEJUELA e OSSER, 2016). Não parece haver melhores resultados com o tratamento combinado (uso da medicação associada à terapia) em comparação à um tratamento isoladamente (CRITS-CHRISTOPH et al., 2011). No entanto, indiferente do tratamento escolhido, normalmente leva de quatro a seis semanas para começar a mostrar algum efeito na melhora do paciente (WILKINS, 2019).

2.2 TAURINA

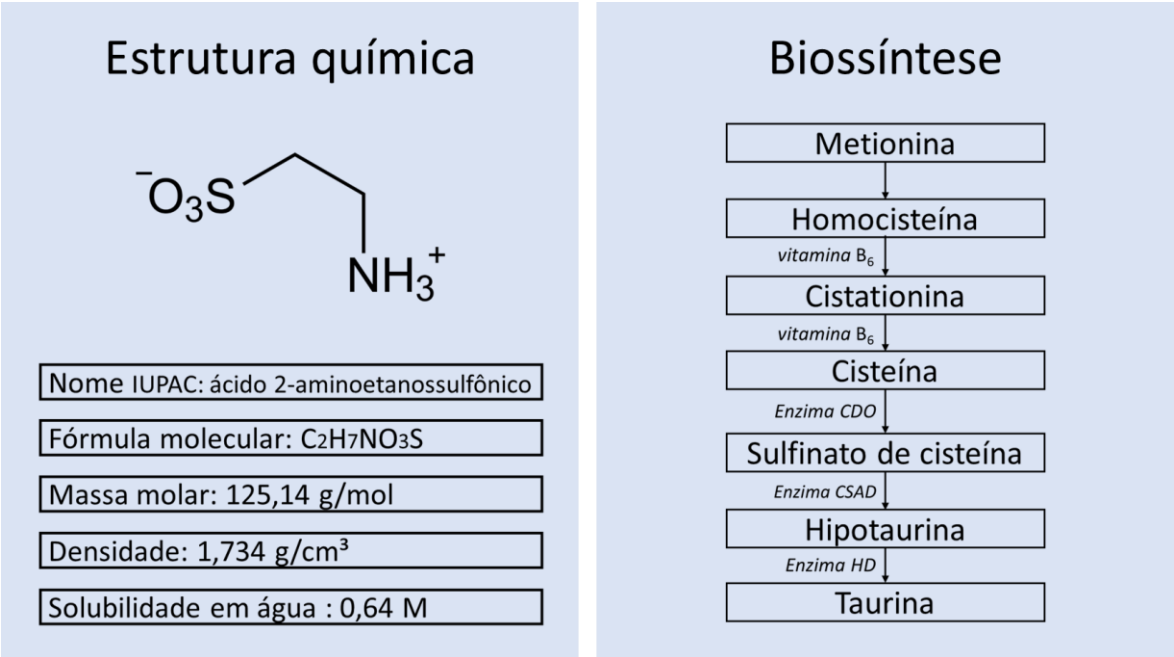
O nome “taurina” derivou do latim *taurus* (referindo-se à espécie *Bos taurus)*, quando foi originalmente isolada da bile de bovinos pelos pesquisadores Friedrich Tiedemann e Leopold Gmelin em 1827 (BIRDSALL, 1998). A taurina apresenta um grupamento sulfônico ($-SO_3$) em sua estrutura molecular, fato que a difere dos demais aminoácidos que possuem um grupamento carboxílico (COOH) (HUXTABLE, 1992; SIRDAH, 2015). Apesar de apresentar características de um aminoácido, a taurina não participa da síntese proteica, sendo frequentemente referida como um aminoácido "não essencial" ou "condicionalmente essencial" (RIPPS e SHEN, 2012). A estrutura química e propriedades[1] da taurina serão mostradas na Figura 4.

[1]As informações sobre as propriedades da taurina estão disponíveis em: pubchem.ncbi.nlm.nih.gov/compound/Taurine.

2.2.1 Biossíntese

A via endógena de biossíntese da taurina em humanos, mostrada na Figura 4, ocorre a partir dos aminoácidos metionina e cisteína, através de reações de oxidação e transulfuração (DE LA PUERTA et al., 2010; SIRDAH, 2015). A primeira reação consiste na oxidação do grupo sulfidril da cisteína em sulfinato de cisteína pela enzima cisteína dioxigenase (CDO). Na segunda parte da reação, o sulfinato de cisteína é descarboxilado em hipotaurina pela enzima cisteína sulfinato descarboxilase (CSAD). Por fim ocorre a conversão à taurina através da hipotaurina desidrogenase (HD) na etapa final. Para que estas reações ocorram, deve-se haver a presença de vitamina B_6 (DE LUCA et al., 2015).

Figura 4 - Propriedades e biossíntese da taurina



Fonte: autoria própria.

Os principais locais de síntese de taurina são o fígado e o SNC, devido a maior produção de enzimas CDO e CSAD nesses órgãos. Contudo, essas enzimas já foram encontradas no tecido adiposo branco, rins e testículos, sugerindo outros locais de síntese (BOUCKNOOGHE et al., 2006). Devido a insuficiente produção endógena de taurina em humanos, a ingestão de alimentos de origem animal e marinha ricos em taurina é fundamental (SZYMANSKI e WINIARSKA, 2008).

2.2.2 Absorção, Distribuição e Excreção

A absorção da taurina pela dieta (via exógena) ocorre nas células do trato gastrointestinal, captada pelo transportador de taurina de alta afinidade denominado ‘taurine transporter’ (TauT, gene SLC6A6) e/ou de baixa afinidade ‘proton-coupled amino acid transporter 1’ (PAT1, gene SLC36A1) (RIPPS e SHEN, 2012; LAMBERT et al., 2015). O transportador TauT pode ser modulado pela proteína quinase C (PKC), responsável pela inibição do transporte, assim como pela proteína quinase A (PKA), que irá estimular ou inibir o transporte de taurina, dependendo do tecido. Ambas enzimas são sensíveis à concentração de Ca^{2+} (HAN et al., 2006; HAN et al., 2016).

O fluxo de taurina em diferentes tipos celulares é inibido por bloqueadores de canais aniônicos, sugerindo ser mediado por um sistema de transporte mais similar a um canal iônico do que um transportador (SHEN et al., 2002). O efluxo da taurina é passivo e direcionado pelo gradiente de concentração. Dois canais são investigados para essa função: o canal aniônico sensível a osmólitos orgânicos (VSOAC), e o canal aniônico regulado por volume (VRAC) (LAMBERT et al., 2015). Há indícios de que o efluxo da taurina esteja associado a canais aniônicos ativados pelo aumento de volume VRAC. No entanto, ainda não se sabe, precisamente, por quais vias a taurina é liberada pelas células (HOFFMANN et al., 2009).

Após ser absorvida, a taurina é distribuída para diversos órgãos por meio de transporte ativo, regulado pelo gradiente de concentração. Uma parcela da taurina ingerida será utilizada pelo fígado para a conjugação com ácidos biliares, e produção de sais biliares, ou ainda excretada pelas vias renais. Portanto, o conteúdo total de taurina no organismo é proveniente de três maneiras diferentes: (1) ingestão direta de taurina pela dieta; (2) síntese de novo de taurina pelo fígado e outros tecidos; e (3) reabsorção renal (LAMBERT et al., 2015) (BOUCKNOOGHE et al., 2006). Ao final disso, a taurina será excretada nas fezes quando conjugada com ácidos biliares, ou eliminada pela urina através dos rins quando não conjugada, uma vez que não pode ser metabolizada pelos mamíferos devido ausência de enzimas (LAMBERT et al., 2015).

2.2.3 Concentrações Celulares

As concentrações de taurina no meio extracelular são inferiores às relatadas intracelularmente, variando de 10 a 100 μM (HUXTABLE, 1992; SCHULLER-LEVIS e PARK, 2003; MARCINKIEWICZ e KONTNY, 2014; DE LUCA et al., 2015). Os efeitos extracelulares da taurina são atribuídos à ativação de alvos celulares específicos em concentrações muito baixas (HUXTABLE, 1992). Os níveis intracelulares de taurina são mais elevados em tecidos com maior atividade oxidativa, tais como o cérebro (30-40 mM), o coração (25-30 mM), o pulmão (11-17 mM), e o fígado (em torno 10 mM) (GREEN et al., 1991; STURMAN, 1993; MASSIEU et al., 2004; HANSEN et al., 2006; OLIVEIRA et al., 2010). Uma explicação para essa diferença de concentração entre os meios intracelular e extracelular é devido à ausência do grupo carboxila que não permite sua incorporação às proteínas, torna-a um osmólito intracelular livre (STURMAN e CHESNEY, 1995; HAN et al., 2006).

2.2.4 Funções Biológicas

A taurina é um osmólito orgânico conhecido por fornecer substrato para a formação de sais biliares e pela função de regulação do volume celular. Contudo, ela também atua na modulação da concentração intracelular de Ca^{2+}, sendo um dos aminoácidos mais abundantes em diversos órgãos como o cérebro, a retina, e o tecido muscular (HUXTABLE, 1992; RIPPS e SHEN, 2012). Portanto, a deficiência de taurina está associada às anormalidades no desenvolvimento cerebral, aos danos graves em neurônios da retina, à cardiomiopatia, e o prejuízo da função renal (RIPPS e SHEN, 2012).

A taurina desempenha diferentes funções fisiológicas, as quais são bem descritas na literatura. Dentre as principais, pode-se citar a osmorregulação, a estabilização de membrana, a ação hipoglicemiante, a neuromodulação, e o efeito protetor sobre o estresse oxidativo e processos inflamatórios. Os principais efeitos biológicos da taurina, os mecanismos associados, e as respectivas referências estão descritos na Tabela 1.

Tabela 1 - Efeitos biológicos da taurina

Efeitos	Principais Mecanismos	Referências
Osmorregulação	• Via angiotensina II	(DE LUCA et al., 2015) (SCHAFFER et al., 2010)
Neuromodulação	• Via ativação de receptores $GABA_A$, glicina, e inibição de receptores NMDA • Contra a excitotoxicidade do glutamato	(WU e PRENTICE, 2010) (MENZIE et al., 2014)
Estabilização de membrana	• Via enzima que controla a proporção PE: PC nas membranas	(HAMAGUCHI et al., 1991) (LAMBERT et al., 2015)
Regulação do Ca^{2+} intracelular	• Por retardar o influxo de Ca^{2+} no citosol em neurônios	(FOOS e WU, 2002)
Ação antioxidante e anti-inflamatória	• Conversão de superóxido ($O2^{\bullet-}$) como o ácido hipocloroso em taurina cloramina • Via inibição de citocinas pró-inflamatórias por haloaminas[2] de taurina	(LERDWEERAPHON et al., 2013) (MARCINKIEWICZ e KONTNY, 2014)
Ação hipoglicemiante	• Via secreção de insulina das células β, e sensibilização da insulina nos receptores	(DE LA PUERTA et al., 2010)

Abreviaturas: PE: fosfatidiletanolamina; PC: fosfatidilcolina.

[2]Corresponde à taurina-cloramina, taurina-bromamina e taurina-dibromamina. A taurina neutraliza os compostos tóxicos, produzindo as haloaminas, que são moléculas mais estáveis e menos tóxicas.

2.2.4.1 Mecanismos de Ação da Neuromodulação

A taurina é capaz de ativar o complexo receptor ácido γ-aminobutírico do tipo A ($GABA_A$), receptores de glicina sensíveis à estricnina (ZHANG e KIM, 2007) e inibir o receptor glutamatérgico ionotrópico N-metil-D-aspartato (NMDA) (CHAN et al., 2014). Apesar dos mecanismos subjacentes aos efeitos centrais da taurina ainda não estarem completamente elucidados, sabe-se que ela tem grande importância para o desenvolvimento e crescimento normal do SNC (NEURINGER e STURMAN, 1987; CHESNEY et al., 1998).

Especula-se que a taurina possa modular vias de transdução de sinal e antagonizar os efeitos do glutamato, prevenindo a excitotoxicidade. Os neurônios seriam protegidos da excitotoxicidade glutamatérgica pela redução do nível intracelular de cálcio livre (Ca^{2+}), através da inibição do transportador reverso de Na^{+}-Ca^{2+}, sugerindo potencial interação entre o receptor de taurina e NMDA (WU et al., 2005; MENZIE et al., 2014). Porém, uma vez que um receptor específico para taurina ainda não foi descrito, a compreensão dos seus mecanismos extracelulares é complexa (DELLA CORTE et al., 2002).

2.2.5 Potencial Terapêutico da Taurina em Doenças Neuropsiquiátricas

A taurina também é descrita como um neurotransmissor inibitório, por ser uma substância cerebral endógena com propriedades neuromodulatórias (WU e PRENTICE, 2010; CHAN et al., 2014). No entanto, ela não pode ser classificada como um neurotransmissor clássico, devido à falta de evidências sobre seu armazenamento em vesículas sinápticas, e incerteza da existência de um específico receptor para taurina no SNC de vertebrados (RIPPS e SHEN, 2012). Contudo, devido a pluralidade de suas funções, incluindo prevenção à excitotoxicidade do glutamato, regulação do cálcio Ca^{2+} e do estresse oxidativo, a taurina pode servir como um alvo terapêutico para diversas doenças neuropsiquiátricas, tais como doenças neurodegenerativas, epilepsias, esquizofrenia e relacionadas ao estresse.

2.2.5.1 Efeitos da Taurina em Transtornos Mentais

Pacientes com transtornos mentais apresentam significativos sintomas de ansiedade, estresse e comprometimento cognitivo como comorbidade comum. Em pacientes com esquizofrenia e autismo, a taurina tem mostrado resultados positivos como terapia adjuvante para melhorar a disfunção cognitiva (OMURA et al., 2015; O'DONNELL et al., 2016). Em um estudo com camundongos idosos, foi sugerido que a suplementação crônica de taurina pode corrigir declínio das funções cognitivas relacionado à idade. A taurina aumentou os níveis de GABA, glutamato, a expressão da enzima glutamato descarboxilase, e neuropeptídeo somatostatina, melhorando déficits de memória (EL IDRISSI, 2008).

Em relação ao potencial da taurina frente à neurobiologia do estresse e ansiedade, os estudos são mais centralizados em modelos animais com roedores. O tratamento com taurina já demonstrou ter efeito protetivo contra deficiências cognitivas causadas por estresse (FRANCONI et al., 2004; JIA et al., 2016; SUN et al., 2018), além de ação antidepressiva e ansiolítica (MATTUCCI-SCHIAVONE e FERKO, 1985; WU et al., 2008; EL IDRISSI et al., 2009). A pré-administração de taurina também mostrou reduzir os níveis de dopamina, 5-hidroxitriptamina e noradrenalina, e reverter os níveis elevados de glutamato e corticosterona (MATTUCCI-SCHIAVONE e FERKO, 1985). Embora a influência da taurina na neurobiologia do estresse e ansiedade ainda não seja totalmente compreendida, esses dados sugerem que as diferentes modulações causadas pela taurina podem ser abordagens terapêuticas para os transtornos mentais relacionados ao estresse. Assim, os estudos que visam desvendar as vias moleculares subjacentes às respostas fisiológicas da taurina tornam-se interessantes nas áreas de farmacologia e neurociência comportamental.

2.3 PEIXE-ZEBRA

O uso de modelos alternativos, como o peixe-zebra, tem se destacado nos estudos de desenvolvimento farmacológico, toxicológico e áreas da neurociência. O peixe-zebra (*Danio rerio*) é um peixe teleósteo nativo de água doce do sul e sudeste da Ásia, que vem ganhando destaque na comunidade científica devido sua fácil manutenção, baixo custo e alto potencial para estudos translacionais em vertebrados (RICO et al., 2011; PARKER et al., 2012; STEWART et al., 2014).

2.3.1 Modelagem de Doenças Humanas

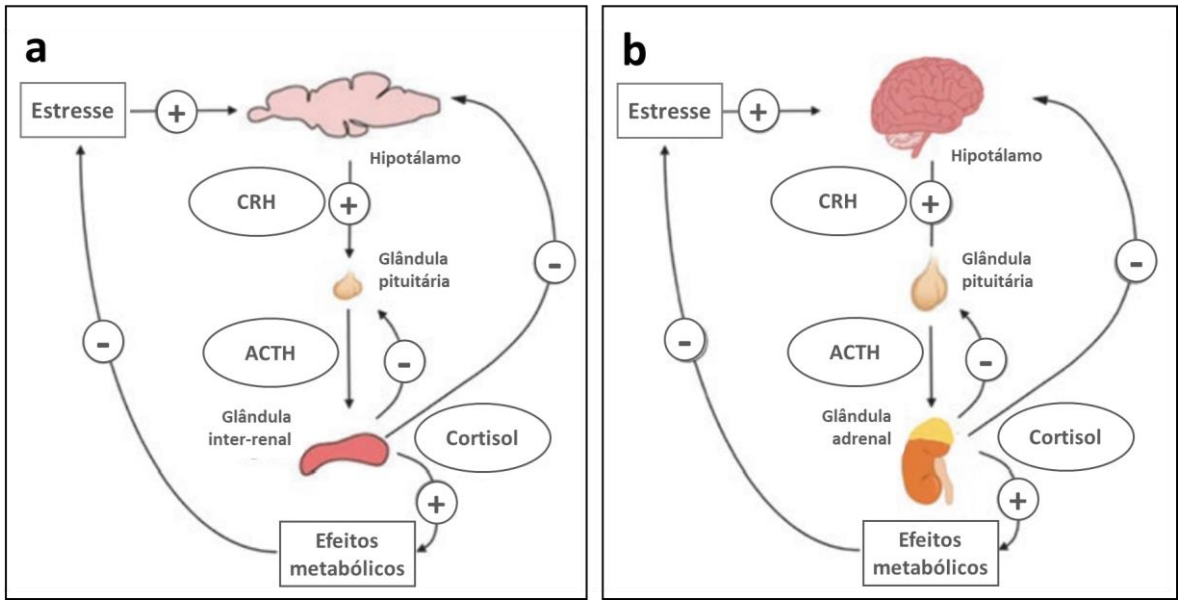
O peixe-zebra tem se fortalecido quanto à modelagem de doenças humanas pelo seu genoma recentemente sequenciado (HOWE et al., 2013). Cerca de 71% dos genes partilham um elevado grau de semelhança (±70%) com os ortólogos de mamíferos (MACRAE e PETERSON, 2003; CHAKRAVARTHY et al., 2014). Desse modo, é presumível que o peixe-zebra seja capaz de realizar tomadas de decisões, mostrando respostas comportamentais quando desafiados a agentes farmacológicos (SISON et al., 2006; PARKER et al., 2012; OLIVEIRA et al., 2013). Diversos modelos de doenças são empregados para o estudo de alterações neurocomportamentais, tais como: modelo de doença de Alzheimer (MUSA et al., 2001; JOSHI et al., 2009), de Parkinson (BRETAUD et al., 2004; SARATH BABU et al., 2016), de epilepsias (ESCAYG e GOLDIN, 2010; HORTOPAN e BARABAN, 2011), de esquizofrenia (SEIBT et al., 2010; SEIBT et al., 2011; SEIBT et al., 2012), e de transtornos relacionados ao estresse (PIATO et al., 2011; DAL SANTO et al., 2014; QUADROS et al., 2016; CANZIAN et al., 2017).

2.3.2 Regulação do Estresse Emocional

O mecanismo de regulação do estresse emocional do peixe-zebra é muito semelhante ao ser humano. Os efeitos desencadeados pelo estresse podem ser avaliados através das respostas neuroendócrinas após estímulos de estresse (CACHAT et al., 2010). Assim como em mamíferos, o peixe-zebra possui o eixo hipotálamo-pituitária-inter-renal (HPI), que é homólogo ao eixo hipotálamo-pituitária-adrenal (HPA) (NESAN e VIJAYAN, 2016), tendo o cortisol como hormônio primário em ambas as espécies (Figura 5).

A resposta ao estresse evolutivamente conservada entre o peixe-zebra e o homem favorece a validade do modelo para estudar as respostas ao estresse mediadas por cortisol (COLLIER et al., 2017). Análises temporais dos níveis de cortisol no corpo inteiro após um estressor, mostram um aumento linear do cortisol aos 3 min, com pico máximo aos 15 minutos e retorno dos níveis basais próximos aos 60 minutos pós-estressor (BARCELLOS, 2007; RAMSAY, J. M. et al., 2009). Portanto, além das análises comportamentais, as respostas neuroendócrinas, através do cortisol, tornam o peixe-zebra uma valiosa ferramenta no estudo de transtornos relacionados ao estresse e ansiedade (COLLIER et al., 2017).

Figura 5 – Comparativo entre peixe-zebra e ser humano na regulação do estresse



Fonte: imagem adaptada de Collier et al., 2017.

2.3.3 Avaliação Comportamental do Estresse e da Ansiedade

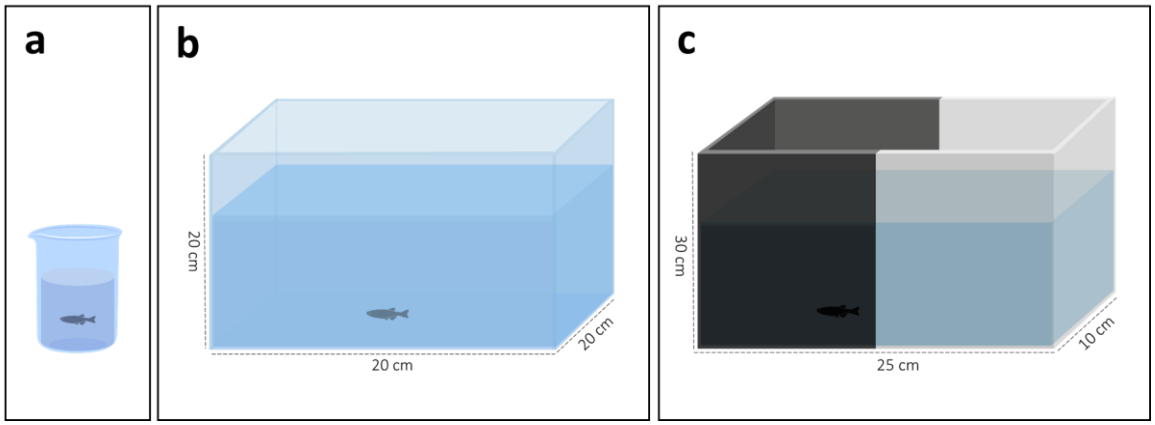
Os estados de estresse e ansiedade em peixe-zebra podem ser medidos através das respostas comportamentais frente à vários estímulos, tais como: compostos ou fármacos, estímulos visuais, físicos, ou químicos (EGAN et al., 2009; MAXIMINO et al., 2018). Os testes comportamentais mais usados para analisar a avalição comportamental de estresse e ansiedade são os testes do novo tanque e o claro-escuro (Figura 6). Ambos se baseiam na resposta do peixe-zebra em explorar ambientes desconhecidos em busca de alimentos, parceiros ou rotas de fuga (EGAN et al., 2009; MAXIMINO et al., 2010; ROSEMBERG et al., 2011; PITTMAN e PIATO, 2017). É importante salientar que a análise integrada de diferentes parâmetros comportamentais por meio dos diferentes testes, aprimora o conhecimento de diferentes variáveis, e auxilia na melhor compreensão dos efeitos que os compostos exercem sob a neurofisiologia do peixe-zebra frente a situações distintas.

O teste de novo tanque é bem validado para a análise do comportamento do tipo ansiedade que envolve medir o congelamento (‘freezing’), e o comportamento exploratório após a sua introdução à um novo tanque (KYSIL et al., 2017). Esse teste baseia-se no instinto natural do peixe em buscar inicialmente a proteção quando colocado em um ambiente desconhecido, inicialmente permanecendo mais tempo no fundo do tanque e evitando a superfície (CACHAT et al., 2010). Este aparato é análogo ao campo aberto em roedores

(KYSIL et al., 2017), onde o peixe-zebra adulto gasta cerca de 50% de uma sessão de 5 minutos no fundo do tanque (Figura 6b) (LEVIN et al., 2007; WONG et al., 2010). Através deste teste, pode-se analisar alterações em alguns parâmetros comportamentais indicativos de ansiedade, tais como: o tempo de permanência no fundo, o tempo de latência para entrada na área do topo, o número de cruzamentos entre as áreas, a distância percorrida, e o tempo e número de episódios de congelamento (KYSIL et al., 2017).

O teste claro-escuro mede o comportamento do tipo ansiedade na forma de escototaxia (preferência pela escuridão), em resposta comportamental do próprio peixe, ou à manipulação farmacológica (COLLIER et al., 2017; KYSIL et al., 2017). O aparato consiste em um tanque com um dos lados escuro e o outro claro, ou seja, revestido com as cores preta e branca (Figura 6c) (SERRA et al., 1999; BLASER et al., 2010; MAXIMINO et al., 2010). Assim, o comportamento do animal a ser analisado pode ser modulado por agentes farmacológicos, que podem ser adicionados diretamente na água de um tanque ou béquer (Figura 6a) antes do teste comportamental. Como resultado da análise farmacológica, um maior tempo de permanência na zona clara, e uma menor latência para entrada nessa área, podem ser indicativo de uma redução no comportamento do tipo ansiedade (MAXIMINO et al., 2010; KYSIL et al., 2017).

Figura 6 – Aparatos de avaliação comportamental de estresse e ansiedade



Fonte: autoria própria. Béquer de exposição farmacológica (a), aparato do teste de novo tanque (b) e aparato do teste claro-escuro (c).

3 JUSTIFICATIVA

Os transtornos mentais são um dos maiores problemas de saúde pública mundial. O processo entre o diagnóstico, a escolha de um tratamento eficaz, e a sua disponibilidade no sistema de saúde, é complexo e muitas vezes demorado. Por isso, a busca de novas estratégias farmacológicas para o tratamento desses transtornos é fundamental para resolução desse problema de saúde pública. A taurina tem sido estudada como terapia adjuvante para diversas disfunções do SNC, principalmente devido sua propriedade de neuroproteção contra à excitotoxicidade do glutamato, regulação do cálcio, dos processos inflamatórios e estresse oxidativo.

4 OBJETIVO GERAL

Analisar a modulação neurocomportamental das ações da taurina como tratamento dos transtornos mentais em humanos por meio do peixe-zebra como organismo modelo.

4.1 OBJETIVOS ESPECÍFICOS

i. Revisar sistematicamente se o peixe-zebra é um organismo modelo em potencial no estudo dos efeitos terapêuticos da taurina em modelos de transtornos do SNC;
ii. Investigar se a taurina modula as respostas comportamentais do tipo ansiedade em peixe-zebra;
iii. Verificar se a taurina modula as respostas comportamentais e neuroendócrinas do estresse em peixe-zebra.

5 ARTIGOS CIENTÍFICOS

Nesse capítulo serão apresentados os três artigos que compõem este estudo.

O primeiro artigo compreende uma revisão sistemática publicada no periódico ‘Neuroscience and Biobehavioral Reviews’ (Qualis A1 em Ciências Biológicas II com fator de impacto de 8,002) sobre a utilização do peixe-zebra como organismo modelo para os estudos dos efeitos da taurina no SNC.

Os dois últimos trabalhos compreendem artigos científicos originais regulares publicados em dois periódicos diferentes. Um artigo foi publicado em ‘Neuroscience Letters’ (Qualis A4 em Ciências Biológicas II com fator de impacto de 2,173), e o outro artigo foi publicado em ‘Hormones and Behavior’ (Qualis A1 em Ciências Biológicas II com fator de impacto de 3,949). Nesses dois artigos foram descritas as respostas de ansiedade e estresse moduladas pela taurina em peixe-zebra.

5.1 ARTIGO 1

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Understanding taurine CNS activity using alternative zebrafish models

Nathana J. Mezzomo, Barbara D. Fontana, Allan V. Kalueff, Leonardo J. G. Barcellos, Denis B. Rosemberg

Abstract

Taurine is a highly abundant "amino acid" in the brain. Although the potential neuroactive role of taurine in vertebrates has long been recognized, the underlying molecular mechanisms related to its pleiotropic effects in the brain remain poorly understood. Due to the genetic tractability, rich behavioral repertoire, neurochemical conservation, and small size, the zebrafish (*Danio rerio*) has emerged as a powerful candidate for neuropsychopharmacology investigation and in vivo drug screening. Here, we summarize the main physiological roles of taurine in mammals, including neuromodulation, osmoregulation, membrane stabilization, and antioxidant action. In this context, we also highlight how zebrafish models of brain disorders may present interesting approaches to assess molecular mechanisms underlying positive effects of taurine in the brain. Finally, we outline recent advances in zebrafish drug screening that significantly improve neuropsychiatric translational research and small molecule screens.

KEYWORDS: Brain disorder; Neural function; Neuropsychopharmacology; Taurine; Zebrafish

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Review

Understanding taurine CNS activity using alternative zebrafish models

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Zebrafish
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Neuropsychopharmacology
Brain disorder

ABSTRACT

Taurine is a highly abundant "amino acid" in the brain. Despite the potential neuroactive role of taurine in vertebrates has long been recognized, the underlying molecular mechanisms related to its pleiotropic effects in the brain remain poorly understood. Due to the genetic tractability, rich behavioral repertoire, neurochemical conservation, and small size, the zebrafish (*Danio rerio*) has emerged as a powerful candidate for neuropsychopharmacology investigation and *in vivo* drug screening. Here, we summarize the main physiological roles of taurine in mammals, including neuromodulation, osmoregulation, membrane stabilization, and antioxidant action. In this context, we also highlight how zebrafish models of brain disorders may present interesting approaches to assess molecular mechanisms underlying positive effects of taurine in the brain. Finally, we outline recent advances in zebrafish drug screening that significantly improve neuropsychiatric translational researches and small molecule screens.

1. Introduction

Taurine (2-aminoethanesulfonic acid, $NH_2CH_2CH_2SO_3H$) is one of the most abundant amino acids in various tissues, including the brain (Xu et al., 2008; Schaffer et al., 2010). Unlike the classical amino acids, taurine has a sulfonic acid (instead of a carboxylic acid) in its chemical structure. As an amino sulfonic acid, taurine is not incorporated into proteins and occurs freely *in vivo* (Huxtable et al., 1992; Sirdah, 2015; Suárez et al., 2016). Since taurine is synthesized endogenously from methionine and cysteine in the presence of vitamin B_6, it is considered a "semi-essential amino acid" in humans (Puerta et al., 2010; Das et al., 2012; Sirdah, 2015).

The biosynthesis of taurine is highly variable between individuals depending on nutritional state, protein intake, and cysteine accessibility (Huxtable, 1992; de Luca et al., 2015). The availability of cysteine is dependent on the metabolic equilibrium between homocysteine and methionine, via folic acid, vitamin B_{12} and the enzyme activity of methyltetrahydrofolate reductase (de Luca et al., 2015). Since biosynthetic capacity of taurine is limited in humans, an alternative source is dietary intake with meat and seafood (Salze and Davis, 2015).

In humans, intracellular concentrations of taurine range between 5 and 20 μmol/g in various tissues, including cardiac muscle, retina, skeletal muscle, and brain (Huxtable, 1992; Ripps and Shen, 2012; de Luca et al., 2015). However, some other mammals do not naturally produce taurine due to the lack of the key enzyme for its biosynthesis, thereby necessitating dietary supplementation to avoid taurine deficiency, which can trigger retinal degeneration (Hayes et al., 1975) and immunological deficits (Levis et al., 1990). Taurine plays a pleiotropic role by modulating osmoregulation (Schaffer et al., 2010), membrane stability (Lambert et al., 2015), intracellular calcium metabolism (Foos and Wu, 2002) and neuronal activity (Wu and Prentice, 2010). Additionally, taurine prevents oxidative stress (Lerdweeraphon et al.,

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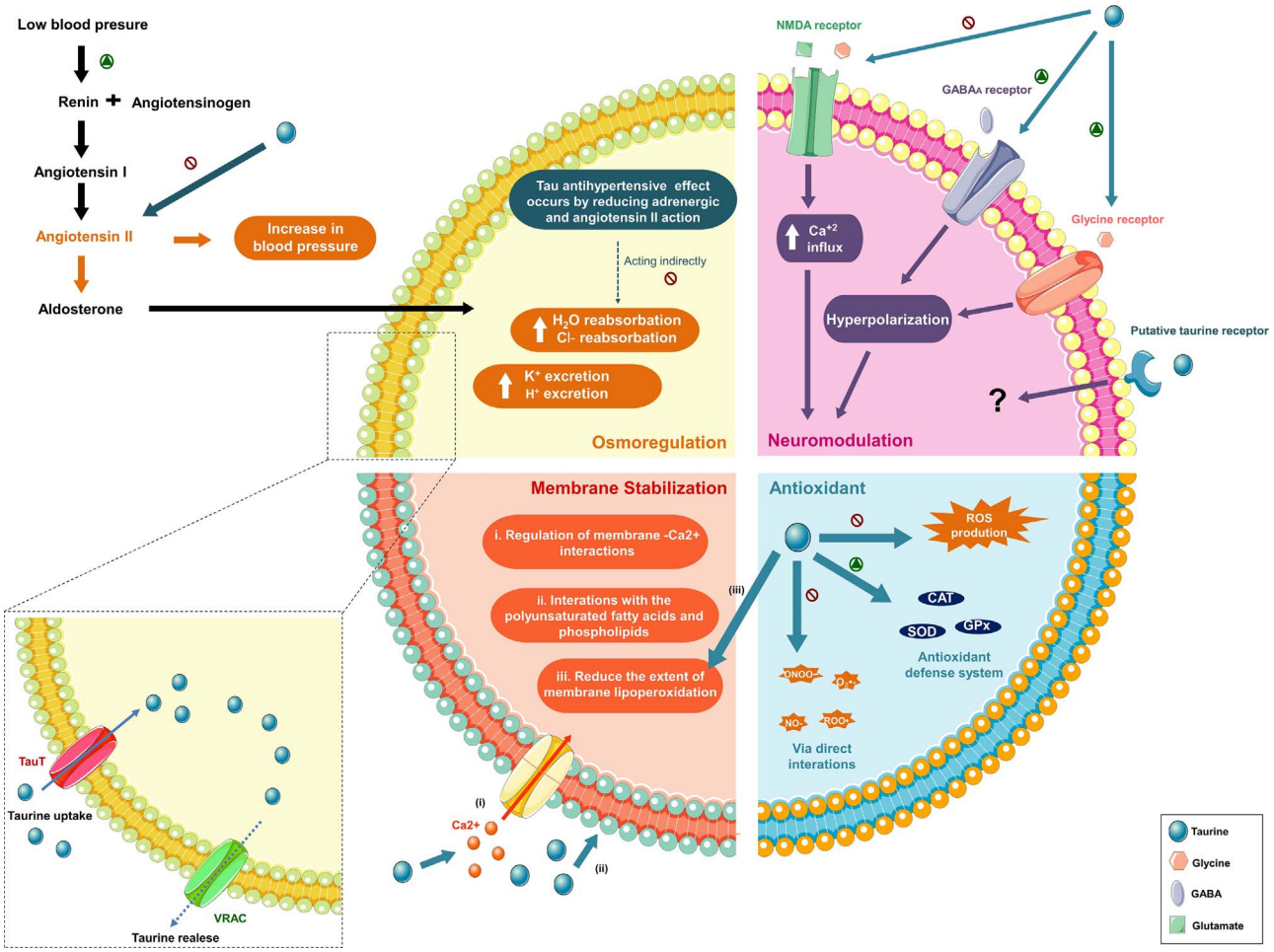

Fig. 1. Mechanisms of taurine action *in-vivo* include its role in osmoregulation, neuromodulation, membrane stabilization and antioxidant defense. The cartoon illustrates taurine transporters **(TauT and VRAC)**, as well as the putative taurine receptor, and the potential modulatory effects of taurine in the brain.

2013) and inflammation (Marcinkiewicz and Kontny, 2014), also acting as an endogenous neuroprotector (Menzie et al., 2014). Taurine uptake in mammalian cells is mediated by its specific transporter (TauT, or SLC6A6), which is responsible for regulating taurine levels in a Na^+- and Cl^--dependent manner (Chen et al., 2004). However, the mechanisms involved in taurine release from the cells are still under debate. A major point is whether taurine is released from astrocytes and neurons via a volume-sensitive leak pathway, which is permeable to a range of organic osmolytes (Banerjee et al., 2008; Hansen et al., 2012). Since the exact mechanisms associated with taurine effects are unclear, studies aiming to unravel the molecular pathways underlying the physiological responses of taurine using various experimental models become important.

Recent studies have validated new models for drug screening, target identification, pharmacology, and toxicology to understand the molecular basis of human diseases (Dooley and Zon, 2000; Parng et al., 2002; Sumanas and Lin, 2004; Nishimura et al., 2015). Here, we will focus on the potential application of the zebrafish (*Danio rerio*) in exploring the neurobiological effects of taurine and its mechanisms of action. We emphasize that zebrafish arises as a novel alternative/complementary model organism that may help to generate cross-species and cross-domain translational insights into neuropsychiatric research.

2. Putative mechanisms of taurine in biological systems

2.1. General overview

In 1827, a molecule from ox bile was isolated as Gallen-Asparagin (Tiedemann and Gmelin, 1827). However, the first report related to its current name, taurine, derived from the name of species *Bos taurus* and appeared only a decade later (Demarcay, 1838). The biosynthesis of taurine via the cysteine sulfinic acid pathway was reported in 1962 (Sumizu, 1962). Initially recognized functions of taurine were limited to bile salt synthesis, osmoregulation in marine invertebrates, energy storage in marine worms, and inhibition of the central nervous system (CNS) (Sumizu, 1962; Jacobsen and Smith, 1968). Although taurine was discovered two centuries ago, its several mechanisms of action and physiological relevance have been examined and recognized only four decades ago. Thus, a complete understanding of the mechanisms underlying central effects of taurine has been slow and fragmental.

In vivo, taurine is absorbed by the intestine and it is released into the blood stream presumably by a putative non-saturable pathway (Roig-Pérez et al., 2005; Lambert et al., 2015). Once it reaches the circulation, taurine is distributed between cells, transported by the plasma membrane transporters TauT (encoded by *SLC6A6*) and/or by the proton-coupled amino acid transporter 1 (PAT1, encoded by *SLC36A1*) (Ripps and Shen, 2012; Lambert et al., 2015). The concentrations of taurine in extracellular fluids are lower than those reported intracellularly, ranging from 10 to 100 μM (Huxtable, 1992; Schuller-Levis and Park, 2003; Marcinkiewicz and Kontny, 2014; de Luca et al., 2015). The extracellular effects of taurine are attributed to the activation of specific cellular targets at very low concentrations (Huxtable, 1992). Intracellular taurine levels are higher in tissues with considerable oxidative activity, such as heart (25–30 mM), lung (11–17 mM), and brain (30–40 mM) (Green et al., 1991; Sturman, 1993; Massieu et al., 2004; Hansen et al., 2006; Oliveira et al., 2010). *Post-mortem* analyses showed

a similar distribution of taurine in human brain tissue (ranging from 0.74–1.45 μmoles/g wet tissue), suggesting a widespread location of taurine in the CNS structures (Okumura et al., 1960). Despite taurine is considered an end metabolic product, its convertion into isethionic acid (2-hydroxyethane sulfonic acid) levels in the dog heart *in vitro* and in the rat heart and brain was described (Peck and Awapara, 1967; Read and Welty, 1962). However, taurine excess is usually excreted in the urine or in the bile (Cho et al., 2000). Besides its conjugation with cholic acid, taurine has been reported in several other bound forms, such as N-methyl-taurine, taurobetaine, and *N*-(1-carboxyethyl)-taurine (Machlin and Pearson, 1957). The main functions of taurine, including neuromodulation, osmoregulation, membrane stabilization and antioxidant capacity, are summarized in Fig. 1.

2.2. Neuromodulation

Mounting evidence shows that the neuromodulatory action of taurine is due to its agonistic modulatory effects on central gamma-aminobutyric acid $(GABA)_A$ and glycine receptors (Zhang and Kim, 2007; Poleszak et al., 2011; Chan et al., 2014). For example, taurine can protect neurons from excitotoxicity by lowering the intracellular level of free calcium via inhibiting the reverse mode of Na^+–Ca^{2+} exchanger, suggesting a potential interaction between taurine and N-methyl-D-aspartate (NMDA) receptor (Wu et al., 2005; Menzie et al., 2014). Chan et al. (2014) showed that taurine can inhibit NMDA receptors via multiples mechanisms to reduce glutamate-induced neurotoxicity. Since a specific taurine antagonist has not yet been described, this complicates the understanding of its specific extracellular mechanisms (Della Corte et al., 2002). In the cerebellum, taurine increases the Cl^- conductance in excitable membranes, causing hyperpolarization in neurons and reducing their excitability (Conte-Camerino et al., 1987). These data strongly support the idea that taurine may modulate several second messenger systems and counteract the actions of glutamate, thereby preventing excitotoxicity.

2.3. Osmoregulation and membrane stabilization

Regulation of cell volume is an intrinsic property of any living cell, which have a tendency to swell or shrink, adjusting their internal osmotic pressure. Volume-regulated ion channels counteract cell swelling due to changes in osmolarity by releasing osmolytes to the extracellular milieu (Hoffmann et al., 2009; Sirianant et al., 2016). Thus, osmoregulation plays a crucial role in normal CNS function during cell growth, division, and migration. Recent data revealed that leucine-rich repeat-containing 8A (LRRC8A) is an essential component of the volume-regulated anion channel (VRAC) in astrocytes (Voss et al., 2014). This channel is permeable for a wide variety of anions, amino acids, and organic osmolytes, such as taurine (Nilius, 2004), which has been suggested as an osmoregulator in various species (Simpson et al., 1959; Walz and Allen, 1987; Oja and Saransaari, 1996). Indeed, hippocampus exposed to oxidative stress showed a significant taurine efflux via VRAC in rodents (Tucker and Olson, 2010). Since taurine release properties were mimicked in synaptosomal preparations, distinct mechanisms and/or cellular sources may release taurine *in vivo* (Haskew-Layton et al., 2008). Moreover, the specific mechanisms of taurine in osmoregulation seem to occur due to an antihypertensive effect via vasodilatation by reducing adrenergic and angiotensin II actions and calcium-induced vasospasm (de Luca et al., 2015).

Taurine also acts as a membrane stabilizer at physiological concentrations (Huxtable and Bressler, 1973), modulating the excitability of neuronal membranes by interfering with membrane-Ca^{2+} interactions. Taurine interacts with sites related to anion transport and water influx (Lazarewicz et al., 1985; Wu et al., 2005; Das et al., 2012) and with the polyunsaturated fatty acids and phospholipids (Yorek et al., 1984). Stabilizing effects on the sarcoplasmic reticulum membranes (Huxtable and Bressler, 1973) and brain synaptosomes (Pasantes-Morales and Moran, 1981; Lazarewicz et al., 1985; Wu et al., 2005) have been reported. One possible mechanism underlying membrane stabilization could be related to changes in phospholipid methyltransferase activity, an enzyme which control phosphatidylethanolamine (PE) and phosphatidylcholine (PC) content in membranes. Hamaguchi et al. (1991) reported that taurine increases PE/PC ratio, leading to alterations of cellular membrane fluidity that improve the resistance.

2.4. Antioxidant activity

Taurine has important intracellular antioxidant functions in different tissues, including neurons (Hansen et al., 2006), where it acts by lowering the production of oxidants and/or boosting the antioxidant protection (Rosemberg et al., 2010; Shimada et al., 2015). *In vitro,* taurine can interact directly with some oxidant radicals (peroxyl radical, anion superoxide, nitric oxide and peroxynitrite) thereby exerting a scavenger effect at physiological intracellular concentrations (Oliveira et al., 2010). During inflammation, stimulated neutrophils release large amounts of taurine that can rapidly react with hypochlorous acid to form taurine-chloramine. This conjugate provides a detoxification mechanism, which protects against neutrophil-induced cytotoxicity (Marcinkiewicz and Kontny, 2014). Taurine-chloramine is taken up into the cells and further concentrated in the mitochondria, where it changes the membrane potential, promotes mitochondrial swelling, and triggers apoptosis via caspase-9 activation (Klamt and Shacter, 2005). Moreover, taurine-chloramine has anti-inflamatory activities *per se*, since it inhibits the production of nitric oxid, tumor necrosis factor alpha (TNF-α), IL-6, IL-8, and suppresses NF-kB synthesis (Agca et al., 2014; Kim et al., 2011; Kontny et al., 2000).

Despite its important role in controlling the pro-oxidant-antioxidant balance (Aruoma et al., 1988; Gürer et al., 2001; Parildar-Karpuzoğlu et al., 2008; Das et al., 2012), more studies are needed to explain how intracellular taurine modulates cellular redox profile.

3. The use of zebrafish in neuropsychiatric research

3.1. General aspects

The zebrafish is a freshwater teleost fish native to Southeast Asia. Their small size, easy maintenance, low cost, easy breeding, and translucent embryos were instrumental in introducing the zebrafish to biomedicine (Rico et al., 2011; Parker et al., 2012; Stewart et al., 2014, 2015). Importantly, both larvae and adult zebrafish are easier to care and need a little space to work, constituting important characteristics to perform medium/high throughput screens (Bilotta et al., 1999; Rico et al., 2011; Kalueff et al., 2013). The drug delivery method is also an interesting feature since chemical compounds can be added to the tank water and be promptly absorbed by the immersed zebrafish through gills (Rosemberg et al., 2012; Tran et al., 2015). The zebrafish have already proven to be a powerful animal model for genetic, developmental and pharmacological screening, and they exhibit a diversity of behaviors including social and defensive responses that may be useful for interactive neurophenotyping (Gerlai, 2003; Guo, 2004; Blaser and Vira, 2014).

3.2. Recent approaches of zebrafish use in behavioral neuroscience

The zebrafish promise as an alternative organism for modeling human diseases has been empowered by its recently sequenced genome (Howe et al., 2013). Around 70% of zebrafish genes share a high degree of similarity with their mammalian orthologs (MacRae and Peterson, 2015). Despite considerable neuroanatomical differences between mammalian and teleosts, mounting evidence shows that the zebrafish present several brain areas with homologous functions (Ullmann et al., 2010; Randlett et al., 2015). For example, the lateral pallium of the

telencephalic area of zebrafish is responsible for memory processes, while habenula is associated to fear responses, similar to hippocampus and amygdala, respectively (Perathoner et al., 2016; Agetsuma et al., 2010). Zebrafish are fully capable of cognitive processing and complex decision-making, showing analogous behavioral responses and sensitivity to pharmacological agents (Sison et al., 2006; Parker et al., 2012; Oliveira, 2013).

To extrapolate experimental data from animal models to humans in translational neuroscience, the investigation of different validity criteria is imperative.

Validation of a certain model is a scientific approach that improves its reproducibility and consistency (Vervliet and Raes, 2013). For example, the construct validity evaluates how a specific process, trait or state reflects theoretical assumptions. In other words, it correlates mechanistic similarities between the model and the clinical condition (Willner, 1991). While face validity refers to conserved phenomenological and symptomatological similarities of features, the predictive validity implies the extrapolation of the effects of a certain manipiulation from one species to another (van der Staay and Steckler, 2002; Willner, 1991). Although construct validity has been considered the most important criterion for animal models, both face and predictive validities establish a network association of drug effects, behavioral phenotypes, and etiology to unravel molecular pathways associated with clinical conditions (van der Staay et al., 2009). During the last decade, the predictive, face, and construct validity of different behavioral tasks have been described for zebrafish. Various complex behaviors have already been reported for the species, such as aggression (Gerlai et al., 2000; Fontana et al., 2015), long- and short-term memory (Blank et al., 2009; Cognato et al., 2012; Jia et al., 2014), object discrimination (May et al., 2016) and color preference (Bault et al., 2015). Zebrafish have also been used to investigate behavioral- and molecular-related features of Alzheimer's disease (Bortolotto et al., 2015; Lee and Freeman, 2016), Parkinson's disease (Sarath Babu et al., 2016), schizophrenia (Giacomotto et al., 2016), epilepsy (Grone et al., 2016), obesity (Den Broeder et al., 2015), diabetes (Sarras et al., 2015), endocrinology and other metabolic dysfunctions (Alderman and Vijayan, 2012; Alsop and Vijayan, 2008; Baiamonte et al., 2015). Together, these aspects reinforce the relevance of using zebrafish in translational neuroscience studies as summarized in Table 1 and Fig. 2.

4. Taurine effects in zebrafish models

4.1. General aspects

Early works by Michel and Lubomudrov (1995) have evaluated the specificity and sensitivity of the olfactory organ of adult zebrafish to amino acids, bile acid, and steroid odorants using the electro-olfactogram recording protocol. Although taurine-conjugated bile acids (taurocholic acid, taurochenodeoxycholic acid, taurolithocholic acid-3-sulfate) were more effective odorants than other molecules, later works described the molecular characterization of the receptors for amino acid and bile salt odorants in adult zebrafish. Michel and Derbidge (1997) showed that zebrafish cells express specific odorant receptor gene subfamilies that mediate the chemical perception of taurine-conjugated odorants. David-Watine et al. (1999) isolated a novel subunit (αZ1) of glycine receptor of zebrafish, with a high degree of homology between its amino acid sequence with the mammalian α1 subunit, while M4 and C-terminal domains were more similar to the α2/α3 subunit. Additionally, taurine acts as a potent agonist of αZ1 receptor subunit, suggesting that glycine receptor may mediate its effects in zebrafish.

Zebrafish TauT protein has 625 amino acids and presents a high molecular identity in comparison to the mouse, rat, and human orthologs (72%, 74%, and 73%, respectively). Besides, its heterologous expression in mammalian cells revealed that taurine uptake in zebrafish occurs in a Na^+/K^+–dependent manner and presents substrate selectivity, substrate affinity, ion dependence, and stoichiometry similar to those of mammalian TauTs (Kozlowski et al., 2008). As a maternally derived molecule, TauT mRNA is evident in the 1–4 cell-stage embryo. Later, during embryogenesis, TauT transcripts are detected in the retina, heart, brain, kidneys, and somites (Kozlowski et al., 2008). Furthermore, the zebrafish genome contains two LRRC8A orthologs (named *lrrc8aa*, and *lrrc8ab*) that share 87% identity with human LRRC8A (Yamada et al., 2016). Molecular experiments also revealed that cysteine sulfinic acid decarboxylase (CSAD), the rate-limiting enzyme in the *de novo* biosynthesis of taurine is detected in yolk, syncytial layer, and various embryonic tissues (e.g. notochord, brain, retina, pronephric duct, liver, and pancreas) (Chang et al., 2013). Interestingly, TauT knockdown delays embryo development triggering apoptosis in the brain and spinal cord cells (Kozlowski et al., 2008), while reduced *csad* expression decreases embryonic taurine levels and increases early mortality and cardiac anomalies (Chang et al., 2013). Taken together, these results suggest an evolutionarily conserved function of taurine in vertebrate species, raising the possibility to assess the mechanisms underlying its actions in different cell types.

Neurobehavioral data have shown that zebrafish acutely exposed to taurine at 42, 150, and 400 mg/L displayed an anxiolytic-like profile without changes in locomotion. In addition, 150 mg/L taurine reduced risk assessment episodes, suggesting that, like in rodents, taurine is anxiolytic in zebrafish (Mezzomo et al., 2016). Thus, the use of different experimental models emerges as an interesting approach to clarify the neurochemical pathways associated with taurine effects in CNS.

4.2. Actions of taurine in the acute effects of ethanol

As already mentioned, taurine has important antioxidant properties (Aruoma et al., 1988; Green et al., 1991; Oliveira et al., 2010; Shimada et al., 2015; Patel et al., 2016). Ethanol elevates reactive oxygen species that are strongly associated with many alcohol-related diseases (Albano, 2006). Ethanol can be oxidized by alcohol dehydrogenase, microsomal ethanol oxidation system (MEOS), and catalase. These enzymes produce its reactive metabolite, acetaldehyde, which affects ethanol-mediated responses and impairs the antioxidant defense system (Lieber, 1997; Zima et al., 2001; Quertemont and Didone, 2006; Das et al., 2007).

Recent zebrafish studies show the protective role of taurine in acute ethanol exposure (Rosemberg et al., 2010), as taurine pretreatment lowers acetylcholinesterase activity and lipid peroxidation in fish brain. This suggests that the administration of taurine prior to ethanol maintains redox homeostasis and can modulate the enzyme responsible for terminating the cholinergic transmission *in vivo*. Moreover, similar to mammals, taurine exerts antioxidant and neuroprotective effects in zebrafish.

Further analyses revealed that taurine antagonizes the effects of alcohol in zebrafish (Rosemberg et al., 2012), since it prevents anxiolytic action following a 20-min, and abolished locomotor impairment following a 60-min exposure. Ethanol also influences zebrafish cognition, stress sensitivity, impulsivity, attention, and aggression (Parker et al., 2012). Usually, energy drinks have high levels of taurine and their consumption with alcoholic beverages are common, constituting a public health concern (Marczinski and Fillmore, 2014). Although there is a large body of evidence showing the interactions between energy drinks and ethanol intake, their actions and behavioral effects in different organisms are still controversial. In humans, the ingestion of alcohol plus energy drink attenuated the perception of headache, weakness, dry mouth, and impairment of motor coordination. However, objective measures of motor coordination and visual reaction time, as well as the breath alcohol concentration, did not corroborate these subjective effects (Ferreira et al., 2006). Interestingly, when different doses of energy drinks and ethanol were coadministered in Swiss mice, 10.71 ml/kg of energy drink antagonized the depressant effects of high ethanol doses (Ferreira et al., 2004). Since energy drinks are complex

Table 1
Overview of the experimental protocols for modeling different brain-related disorders in zebrafish.

Brain disorder	Experimental protocol	Mechanism	Characteristics	Reference
Alzheimer's disease	Knockdown for APP, *appa* and *appb*	Antisense morpholino to reduce APP levels in zebrafish embryos.	Induces a defective axonal outgrowth of facial branchiomotor and spinal motor neurons.	Musa et al. (2001), Joshi et al. (2009)
	Knockdown for *psn* genes	Antisense morpholino that led to the loss of *Notch* target gene, *her6* expression and increased expression of *neurogenin 1* (ngn1) mRNA.	Somite defects, defective brain development, altered gene expression and CNS impairments.	Nornes et al. (2003)
	Knockdown for *Pen-2*	Antisense morpholino that led to a reduction of *islet-1* positive neurons.	Induce a p53-dependent apoptotic pathway that contributes to neuronal death.	Campbell et al. (2006)
	Transgenic models (4R-Tau-GFP, 4R/0N tau or TAU- P301L)	Insertion of mutant genes that leads to alterations in TAU protein.	TAU phosphorylation, TAU accumulation resembling tangles and neuronal death.	Tomasiewicz et al. (2002)
	Cholinergic neurotoxins (scopolamine, pilocarpine and physostigmine)	Muscarinic receptor agonist or antagonist, or acetylcholinesterase inhibitor.	Impairs acquisition of passive avoidance response, retention of the learned response and suppressed the electrically evoked field potentials in the telencephalon of the adult zebrafish.	Richetti et al. (2011), Eddins et al. (2010), Kim et al. (2010)
	Glutamatergic neurotoxins (MK-801, ketamine, APV, memantine, kainate, domoate and CNQX)	NMDA-receptor antagonist, KA receptor agonist or AMPA-receptor antagonist.	Induces neuronal damage/death by the over activation of the glutamate receptors.	Swain et al. (2004), Zakhary et al. (2011), Nam et al. (2004), Best et al. (2008), Alfaro et al. (2011), Tiedeken et al. (2005)
Parkinson's disease	Knockdown for *PINK*1	Antisense morpholino to reduce PINK1 levels in zebrafish. PINK1 is second most common cause of autosomal recessive PD.	Decrease in the numbers of central dopaminergic neurons and alterations of mitochondrial function, including increases in caspase-3 activity and reactive oxygen species levels.	Anichtchik et al. (2008)
	Dopaminergic neurotoxins (MPTP, rotenone and paraquat)	Inhibit mitochondrial complex I activity leading to oxidative stress, impaired energy metabolism, proteasomal dysfunction, and, eventually, dopamine neuronal loss.	Decrease in the movement with erratic swimming pattern, increased freezing bouts and change regulation of genes related to PD.	Bretaud et al. (2004), Sarath Babu et al. (2016)
Epilepsy	SCN1A mutant gene	Haploinsufficiency of the voltage-gated sodium channel.	Induces symptoms like Drayet syndrome, including severe cognitive incapacity and high drug-resistant seizure.	Escayg and Goldin, (2010), Saitoh et al. (2012)
	Mind-bomb mutant	Disturbed E3 ubiquitin ligase activity and a downregulation of GABA-related gene transcripts.	Defects of brain development which lead animals to spontaneous seizures when adults.	Hortopan and Baraban (2011)
	OCRL1 homolog mutant gene	The specific mechanics are currently unclear.	Induces symptoms like Lowe syndrome, causing hyperthermia-induced seizures.	Ramirez et al. (2012) Oltrabella et al. (2015)
	GABAergic neurotoxin (PTZ)	$GABA_A$-receptor antagonist.	Induces seizure-like behaviors and abnormal brain physiology.	Baraban et al. (2005), Pineda et al. (2011), Mussulini et al. (2013)
	Glutamatergic neurotoxin (KA)	Increases glutamatergic signaling.	Induces seizure-like behaviors.	Alfaro et al. (2011)
Schizophrenia	Knockdown for *DISC1* and *NRG1*	Impairs specification of olig2-positive cells in the hindbrain and other brain regions	Defects of oligodendrocyte development and loss of olig2-positive cerebellar neurons.	Wood et al. (2009)
	Glutamatergic neurotoxin (MK-801)	NMDA-receptor antagonist.	Causes SCZ-like symptoms, characterized by hyperlocomotion, memory deficits, and social impairments, which can be attenuated by antipsychotics.	Seibt et al. (2010 2011, 2012) Maaswinkel et al. (2013)
Stress-related disorders	Acute stress	Exposure to natural stressors (e.g. alarm substance, chase with netting, restraint stress).	Induce anxiety-like behavior and increase whole-body cortisol levels	Quadros et al. (2016), Canzian et al. (2017), Dal Santo et al. (2014)
	Chronic stress	Exposure to unpredictable natural stressors (e.g. social isolation, exposure to predator, crowding)	Induces anxiety-like behavior, modulates *crf* gene expression, and increases whole-body cortisol levels	Piato et al. (2011)

Abbreviations: AD = Alzheimer's disease; APP = *amyloid-β precursor protein;* APV =class="xps_thinspace" > (2R)-amino-5-phosphonovaleric(2*R*)-amino-5-phosphonovaleric acid; CNQX = 6-cyano-7-nitroquinoxaline-2,3-dione; CRF = Corticotropin Releasing Factor; DISC1 = *Disrupted-in-schizophrenia 1*; KA = Kainic acid; MK-801 = Dizocilpine; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDA = N-methyl-D-aspartate; NRG1 = *Neuregulin*; PD = Parkinson's disease; PEN = *presenilin enhancer;* PINK1 = *putative kinase 1;* PS = *presenilin*; PTZ = pentylenetetrazole; SCN1A = sodium voltage-gated channel alpha subunit 1; SCZ = Schizoprenia.

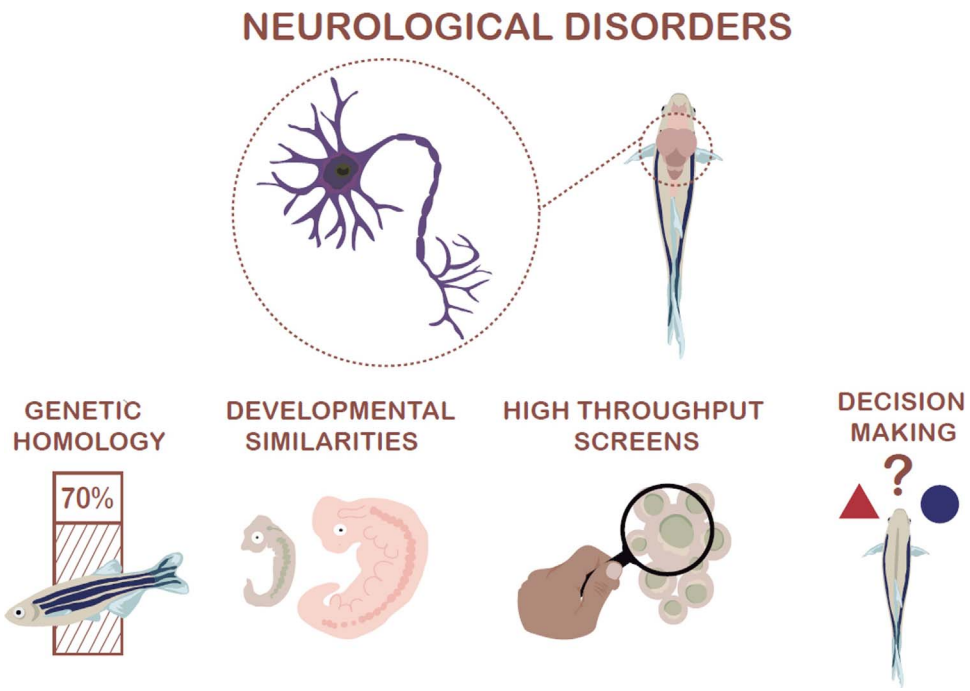

Fig. 2. Schematic diagram showing advantageous features of zebrafish to investigate the underlying mechanisms involved in CNS disorders.

mixtures of taurine, caffeine, and other compounds, it is difficult to state whether these effects result from interaction among molecules or if they are specifically associated with taurine. As agonists of $GABA_A$ receptors promote agonistic behaviors (Miczek et al., 1995, 2003; Zarrabian et al., 2016), the association of taurine and ethanol may influence aggressive behavior. Using the mirror-induced aggression task, Fontana et al. (2015) showed taurine effects in zebrafish cotreated with 0.25% ethanol for 1 h. At 42 and 400 mg/L, taurine increased aggression, whereas 150 mg/L abolished the agonistic behavior, showing a biphasic response for ethanol-induced aggression. Although the mechanisms of taurine neurobehavioral responses are not fully understood, the use of zebrafish continues to foster innovative research into the underlying mechanisms of taurine action and its potential for preventing ethanol-induced CNS deficits.

5. Taurine and neurological disorders

The development of new therapies for CNS disorders is slow, expensive and ineffective (Newman et al., 2011). Furthermore, behavioral biomarkers of neurodegeneration are often challenging to quantify in both clinical and experimental (animal) model systems (Menzie et al., 2014; MacRae and Peterson, 2015; Nunes et al., 2016).

For example, taurine is an endogenous brain substance with robust neuromodulatory properties (Wu and Prentice, 2010; Chan et al., 2014) that has been often described as an inhibitory neurotransmitter. The classic description of neurotransmitter determines that its synthesis must occur in the presynaptic neuron and that the molecule must be stored in synaptic vesicles. A neurotransmitter should be present in the axon terminal at presynapse and its release must be essentially diffused across the synaptic cleft, binding to specific receptors on the postsynaptic side. Importantly, the neurotransmitter released at synaptic cleft must cause changes in the postsynaptic potential and a specific mechanism to remove it from the synaptic cleft should be present (Hanretta and Lombardini 1987; Lodish et al., 2000). Concerning the five basic criteria that allow classifying a certain molecule as a neurotransmitter, several aspects have supported a putative existence of a taurinergic system in the CNS.

First, taurine and/or its synthesizing enzyme are often concentrated presynaptic neuronal terminals (Wu et al., 1979; Wu 1982; Magnusson et al., 1989; Wu and Prentice, 2010). Second, stimulated taurine release occurs both in a calcium-dependent and independent manners (Philibert et al., 1989; Wu and Prentice, 2010). Taurine also modulates neurotransmission by eliciting inhibitory neurotransmission through $GABA_A$ and glycine receptors (Okamoto et al., 1983; Albrecht and Schousboe, 2005; Wu et al., 2008), also inhibiting NDMA receptors (Wu et al., 2005; Menzie et al., 2014; Chan et al., 2014). Specific taurine receptors have been suggested (with a specific Kd in nM range) as distinct from $GABA_A$, $GABA_B$, and glycine receptors, since using agonists or antagonists of these receptors has little effect on taurine binding (Frosini et al., 2003; Wu et al., 1992; Wu and Prentice, 2010). Finally, the CNS expresses transporter systems (TauT and VRAC) able to regulate taurine influx and efflux, respectively (Banerjee et al., 2008; Hansen et al., 2012; Martin 1992; Kozlowski et al., 2008).

In summary, while taurine meets major criteria to be a neurotransmitter in the vertebrate CNS, it cannot yet be classified as a classical neurotransmitter due to unclear storage at synaptic vesicles and a lack of specific cloned taurine receptor. Because neurodegenerative diseases share common fundamental pathophysiology, including glutamate excitotoxicity, calcium imbalance and oxidative stress, which individually or collectively results in cell death (Menzie et al., 2014), taurine may serve as a promising therapeutic target for several neurological disorders.

5.1. Taurine and Alzheimer's disease

The Alzheimer's disease (AD) strongly correlates with synaptic degeneration and neuronal death in limbic structures followed by escalating cognitive decline and social dependence, eventually culminating in death (Caltagirone et al., 2012; Menzie et al., 2014; Carrettiero et al., 2016). It is characterized by the deposition of a 39–43 amino acid residue peptide, amyloid beta (Aβ), in the brains of affected individuals (Louzada et al., 2004; Oz et al., 2009). The neuropathological markers of intracellular neurofibrillary tangles (NFTs) are composed of hyperphosphorylated tau protein and neuronal cell loss, particularly affecting the cholinergic system (Braak and Braak, 1998; Newman et al., 2011; Menzie et al., 2014). Studies reported a strong association between Aβ peptide with AD pathogenesis, and blockade of glutamate receptors prevents Aβ–induced neuronal death (Lipton and Rosenberg, 1994;

Mattson, 2003). Recent data showed that taurine prevents Aβ neurotoxicity via activation of $GABA_A$ receptors (Louzada et al., 2004), suggesting that taurine-related modulation of glutamate and $GABA_A$ receptors can be an interesting therapeutic approach for treating AD.

Because taurine concentrations are 3–4 times higher in the developing than in the mature brain (Miller et al., 2000), it may play a role during brain development and/or aging (Banay-Schwartz et al., 1989). In aged mice, chronic treatment with taurine ameliorates age-dependent memory deficits (El Idrissi, 2008), corroborating the pleiotropic role of exogenous taurine. Indeed, taurine increases the levels of GABA, glutamate, and the expression of glutamic acid decarboxylase (GAD) and neuropeptide somatostatin. As these effects are opposite from those naturally occurring during aging, taurine supplementation may correct age-related decline in cognitive functions (El Idrissi, 2008).

The beneficial properties of taurine have been shown in a transgenic mouse model of AD, rescuing cognitive deficits without affecting cognitively normal mice (Kim et al., 2014). Other studies that employed histopathological tools revealed that taurine increases the proliferation of adult neural stem/progenitor cells from the subventricular zone *in vitro* (Hernandez-Benitez et al., 2012; Ramos-Mandujano et al., 2014), showing a potential role in adult neurogenesis. Furthermore, taurine also reduced activated microglia and increased the survival of newborn neurons, resulting in a net increase of neurogenesis in adult specimens (Gebara et al., 2015). Together, these data support a beneficial role of taurine in hippocampal neurogenesis during brain aging *in vivo*.

Some pharmacological agents, such as donezepil, rivastigmine tartrate, galantamine HBr, memantine, and the psychostimulant modafinil, have been used as cognitive enhancers (Mehlman, 2004). Considering the lack of effective treatments, questions regarding the validity and utility of the existent animal models have emerged. Mice are the dominant vertebrate model for modeling AD-related phenotypes but the use of non-mammalian organisms emerges as a simple strategy for assessing neuropsychiatric disorders. Transgenic, knockout, and morpholino zebrafish models have allowed a better understanding of the genetic mechanisms associated with CNS dysfunctions (Tomasiewicz et al., 2002; Paquet et al., 2009; Formella et al., 2012), thereby serving as valuable tools to investigate the effects of taurine in forward genetics.

The zebrafish cells express genes correspondent to those mutated in human familial AD, amyloid-β precursor protein (APP), *appa* and *appb* (Musa et al., 2001; Joshi et al., 2009; Newman et al., 2011). Orthologs to human of presenilin (PSEN1 and PSEN2), *psen1* and *psen2*, respectively (Wilson and Lardelli, 2013) and prion protein (PRP), *prp1*, and *prp2* have also been described (Kaiser et al., 2012). The loss of zebrafish *appa* and *appb* function by morpholino knockdown resulted in reduced body length and defective convergent extension movements during gastrulation in embryos. These defects are rescued by wild-type human amyloid-β precursor protein mRNA, but not by the Swedish mutant amyloid-β precursor protein, known to cause familial AD (Joshi et al., 2009; Xi et al., 2011; Song and Pimplikar, 2012). Injection of antisense morpholino to reduce APP levels in zebrafish embryos caused convergent extension defects, defective axonal outgrowth of facial branchiomotor and spinal motor neurons (Song and Pimplikar, 2012). These set of data demonstrate that zebrafish provide a powerful system to delineate APP functions *in vivo* and to analyze differences in the activity of different mutant forms of the amyloid-β precursor protein.

Taurine may aid cognitive impairment and inhibit Aβ related damages, since it rescued cognitive deficits in APP/PS1 transgenic mouse model of AD for 6 weeks in both Y-maze and passive avoidance tests. In the cortex of APP/PS1 mice, taurine slightly decreased the insoluble fraction of Aβ (Kim et al., 2014). In rodents, taurine is able to recover the memory impairments induced by alcohol, pentobarbital, sodium nitrite, and cycloheximide without any observable effects on other behaviors including motor coordination, exploration, and locomotor activity (Vohra and Hui, 2000). Moreover, studies reported that the intracerebroventricular administration of taurine protects from hypoxia-induced learning impairment (Malcangio et al., 1989). Intravenously administered taurine significantly improves post-injury functional impairments of traumatic brain injury (Su et al., 2014). Taurine is also able to rescue ageing-dependent loss of visual discrimination (Suge et al., 2007) and to ameliorate the cognitive impairment and abnormal acetylcholinesterase activity in streptozotocin-induced dementia model (Javed et al., 2013). Since taurine presents a cognitive enhancing phenotype in mouse models, the zebrafish arises as a logical non-mammalian candidate for studies of taurine role in behavioral and neurocognitive functions.

5.2. Taurine and Parkinson's disease

Parkinson's disease (PD) is recognized as the second most common progressive neurodegenerative disorder after AD (Driver et al., 2009; Shulman et al., 2011; Ricciardi et al., 2015). Patients with PD show degenerative loss of dopaminergic nigrostriatal neurons, intracytoplasmic Lewy bodies (LBs) and intra-axonal Lewy neurites (LNs) composed of fibrillary aggregated α-synuclein (Spillantini et al., 1998). Clinically, PD is a motor disorder dominated by bradykinesia, rigidity, resting tremor, and postural instability responsive to dopaminergic replacement therapy (Calabresi et al., 2013). Besides these motor symptoms, the existence of a cognitive impairment has been largely attributed to an inability to retrieve information from long-term memory storages (Ricciardi et al., 2015) and to a deficit of acquisition (Kehagia et al., 2010).

Similar with other age-related neurodegenerative disorders, the dopaminergic neurons that degenerate in PD express glutamate receptors and are vulnerable to excitotoxicity (Miranda et al., 1997). Despite the crucial role of dopamine in PD pathogenesis, taurine may also be involved by modulating the nigrostriatal system (Bianchi et al., 1998; Zhang et al., 2015). Taurine potently protects neurons in culture against the toxicity of Aβ, glutamate, kainate, and NMDA (El Idrissi and Trenkner, 1999; Louzada et al., 2004). Although the neuroinhibitory actions of taurine in the CNS have long been known (Zukin et al., 1974; Chung et al., 2012; Menzie et al., 2014), its molecular mechanisms are still debated. Some studies suggest taurine neuromodulation of the nigrostriatal system (Bianchi et al., 1996; Ye et al., 1997), as high taurine levels are found in the striatum (Palkovits et al., 1986), substantia nigra (Dray and Straughan, 1974), and in GABAergic terminals from the striatum to the substantia nigra (Bianchi et al., 1998). The age-related decline in taurine concentrations strongly correlates with the striatal dopaminergic loss (Dawson et al., 1999), and changes in taurine concentrations may contribute to neuronal degeneration (Chung et al., 2012). Since taurine may improve the protection of dopaminergic cells via direct and indirect effects on excitotoxicity and by inhibiting the firing of GABAergic cells (Ye et al., 1997), compounds that modulate GABAergic activity should be explored as neuroprotectants against glutamatergic excitotoxicity.

A great advantage of the zebrafish model system is to serve as a tool to provide an *in vivo* test of toxicity and to screen potential protective molecules in a medium-to-high throughput manner. Extensive information is available regarding the CNS pattern and the neurotransmitter systems in zebrafish, which show important similarities to the human CNS (Bretaud et al., 2011; Wager and Russell, 2013). Another interesting feature involves the knowledge about the dopaminergic system in this species, which has already been characterized in both embryonic and adult stages (Panula et al., 2010). Several neurodegenerative diseases have been modeled in zebrafish using mutant forms of MAPT (Bai et al., 2006; Tomasiewicz et al., 2002), SOD1 (Ramesh et al., 2010), and HTT (Williams et al., 2008). It is also possible to observe PD-like phenotypes in zebrafish treated with a DA neuron-selective toxin indicating the existence of functionally equivalent circuitry (Wagner and Russel, 2013). Conversely, the effects of PD neurotoxins or PD genes in zebrafish should be assessed considering the potential impact of variation in genetic contextual on spontaneous

motor behavior, gene expression levels, the number of dopaminergic neurons, susceptibility to neurotoxins, and the effect of gene knockdown (Bretaud et al., 2011). Thus, the zebrafish may serve as a tempting tool to investigate the gene–environment interactions following taurine treatment in order to improve the knowledge about the pathogenesis of PD and possible pharmacological interventions.

5.3. Taurine and epilepsy

Epilepsy is characterized by the recurrence of unprovoked seizures episodes that cause neurological disorders (Fisher et al., 2005; Banerjee et al., 2009). The epileptic seizures seem to occur via common cellular mechanisms and networks (McCormick and Contreras, 2001) involving sudden and abnormal discharges of neurons (Fisher et al., 2005; Dayapoğlu and Tan, 2016). The treatment consists mainly in the administration of conventional anti-epileptic drugs (AED) that act by inhibiting the sodium currents or enhancing of GABAergic inhibition (Czapinski et al., 2005). Since current AEDs do not exert a significant control of seizures in 30% of patients, the search for novel therapeutic molecules is needed (Torres-Hernández et al., 2015).

Taurine may be a useful agent for treating epilepsy since it modulates neurotransmission and inhibits neuronal excitation (Saransaari and Oja, 2008). Elevated taurine is found in serum of patients with epilepsy, while lower amounts are detected in brain tissue (Wilson et al., 1996; Sejima et al., 1997; Gaby, 2007). Moreover, low taurine brain content may prolong seizure activity and correlates with the onset of epileptic episodes (Oja and Kontro, 1983). On the other hand, agents that induce seizures in animal models elevate taurine levels in the brain, suggesting a possible adaptive protective mechanism to counteract glutamatergic excitotoxicity (Vezzani and Schwarcz, 1985).

Although mechanisms of taurine action in epilepsy are not fully understood, it can reduce seizure episodes as a neuroprotectant (Barbeau, 1973; Barbeau et al., 1975; Izumi et al., 1975; Durelli et al., 1976, 1977; van Gelder et al., 1977; Frigyesi and Lombardini, 1979). For example, mice pretreated with 43 mg/kg taurine show longer onset of tonic seizures after kainate administration, also reducing tonic-clonic convulsions, mortality rate, and neuronal cell death in the hippocampus (El Idrissi et al., 2003). The likely role of inhibitory neurotransmission via $GABA_A$ activation and a modulation of calcium influx in the limbic system was further supported *in vitro*, revealing a neuroprotective action of taurine in neuronal cultures against kainic acid excitotoxicity (also see similar results in Junyent et al. (2009)). Finally, since taurine has antioxidant properties, it can play a protective role in epilepsy by modulating intracellular redox profile. In general, seizure episodes induce neurodegeneration, which can be directly associated with the lipid peroxidation of brain membranes and protein carbonylation occurred due to an increased production of free radicals and/or a decrease in the defense mechanisms (Gomes et al., 2011).

Given the potential protective role of taurine in animal models, clinical trials also began (Barbeau and Donaldson, 1973; Pennetta et al., 1977; Mongiovi, 1978; Airaksinen et al., 1980). Anticonvulsant action of taurine in humans (2 weeks 1.5–7.5 g daily) rescued seizures in 5 out of 9 patients (König et al., 1977). Noteworthy, the majority of these studies date to 1970s and all clinical trials had a small number of patients with different types of epilepsies. These studies also failed to characterize variations in taurine doses and to evaluate the possible synergic/additive effects with classical anticonvulsant medications. However, during the last decade, novel models have gaining importance to elucidate the molecular bases that underlie the neurobiology of epilepsy. The genetic screening in zebrafish has been used to identify genes associated with specific disorders and behaviors (e.g. epilepsy). For example, N-Ethyl-*N*-nitrosourea generated model of Dravet syndrome which has a mechanism involved 3 gene mutations: SCN1, SCN8, HCN1. This syndrome represents a severe childhood epilepsy that begins in the first years of life and causes a severe intellectual incapacity, a high drug-resistant seizure and also can cause unexpected deaths. The zebrafish mutant in the SCN1A gene present a haploinsufficiency for the voltage-gated sodium channel which has been considered one of the main mechanisms involved in the evolution of Drayet syndrome in these animals (Escayg and Goldin, 2010; Saitoh et al., 2012; Griffin et al., 2016). The use of zebrafish for modeling monogenic epilepsy disorders is promisor for searching novel candidates to the treatment of epilepsy since these mutants are also sensitive to various clinically used AEDs (Baraban et al., 2013). Another model for epilepsy described is the *mind-bomb* mutant, which displays disturbed E3 ubiquitin ligase activity and a downregulation of GABA-related gene transcripts that result in a defect of brain development, showing spontaneous seizures (Hortopan et al., 2010; Hortopan and Baraban, 2011). Additionally, mutations of the zebrafish OCRL1 homolog gene make the organism propense to undergo hyperthermia-induced seizures (Ramirez et al., 2012; Oltrabella et al., 2015). High-throughput mutagenesis efforts aiming to mutate each gene in zebrafish are already ongoing and will provide an incomparable resource for characterizing additional epilepsy models (Grone and Baraban, 2015; Kettleborough et al., 2013; Moens et al., 2008) and these zebrafish mutants represent important tools for assessing spontaneous seizures in a simple vertebrate system.

Seizure episodes in zebrafish can also be modeled using classical convulsant drugs (e.g. pentylenetetrazole (PTZ) and kainic acid) (Alfaro et al., 2011; Baraban et al., 2005; Mussulini et al., 2013). Animals display abnormal locomotor activity and corkscrew swimming (a behavioral phenotype that closely resembles tonic-clonic seizures). Pineda et al. (2011) studied the brain electrical activity using electroencephalogram (EEG) recordings in adult zebrafish exposed to PTZ for 35 min. The authors observed an increase of high amplitude sharp transients analogous to the human interictal epileptiform discharges (Pineda et al., 2011). Since the seizure-like behavior occurs simultaneously to the alterations of EEG in adult zebrafish exposed to the same PTZ conditions, a direct correlation of abnormal behavior and electrical activity in brain tissue was postulated (Mussulini et al., 2013). Since there are no data regarding EEG recordings in kainic acid model, more studies are necessary to validate this model. In sum, the use of both larvae and adult zebrafish to investigate the effects of taurine represents a refinement of the existent rodent protocols showing a promising relevance to assess the mechanisms of taurine on epileptic models in medium/high throughput feasibilities.

5.4. Taurine and schizophrenia

Schizophrenia is a serious mental disorder characterized by positive (e.g. hallucinations, delusions) and negative symptoms (e.g. social withdrawal, anhedonia). Patients usually present a confused mental state, disruption of social engagement and emotional expression, and lack of motivation (Heinrichs, 2003; Jenkins 2013; Nasyrova et al., 2015). As important regulators of inflammatory response and redox activity, changes in taurine and glutathione (GSH) metabolism are involved in the pathophysiology of schizophrenia (Schuller-Levis and Park, 2003; Haddad and Harb, 2005). Taurine levels are increased in the prefrontal cortex of patients with schizophrenia, and this rise correlates with illness duration (Shirayama et al., 2010). Moreover, altered taurine levels were detected in patients with acute polymorphic psychosis and depression (Nordin and Sjödin, 2006; Samuelsson et al., 2011).

Mounting evidence supports the hypofunction of a subpopulation of cortico-limbic NMDA receptors (Coyle 2006). Given the role of NMDA receptors in the reward circuitry and in substance dependence, it is reasonable to link a dysfunction of the NMDA receptor dysfunction with schizophrenia (Coyle et al., 2002; Coyle and Tsai, 2004; Coyle 2006). In the last decade, the zebrafish have emerged as a model organism in behavioral pharmacology and neuroscience involved in cognitive dysfunction (Blaser and Vira, 2014). Using the zebrafish, researchers may combine genetic strategies (gene knockdown, mutants, transgenics) for

examining the impact of altered dopamine signaling in neuropsychiatric disorders (Souza and Tropepe, 2011). Furthermore, the underlying genetic mechanisms mediating the neurogenesis of the dopaminergic system are also well conserved between zebrafish and mammalian (Filippi et al., 2007; Ryu et al., 2007).

Although atypical brain functioning has been associated with neuropsychiatric and neurodegenerative conditions, there are few animal models available to study behavioral and cognitive deficit so far. The administration of dizocilpine (MK-801), which acts as an antagonist of the NMDA receptor, elicits a behavioral syndrome in rodents, which is similar to schizophrenia symptoms in humans (Clineschmidt et al., 1982; Deutsch et al., 1997). Similarly, zebrafish exposed to MK-801 present psychotic-like hyperlocomotion, which can be attenuated by antipsychotics (Seibt et al., 2010; 2011, 2012; Maaswinkel et al., 2013). Interestingly, MK-801 elicits anxiolytic-like effects and the presence of olanzapine potentiated this effect (Seibt et al., 2010). Another study showed that pharmacological manipulation of glutamate neurotransmission with MK-801 reduces memory formation, but does not affect memory retrieval in short or long-term memory assays in zebrafish larvae (Andersson et al., 2015). Additionally, it is known that changes in social interaction occur in several neuropsychiatric disorders. Zimmermann et al. (2016) investigated the actions of MK-801 on social preference and in the mirror-induced aggression task in zebrafish. The authors showed that MK-801 decreased the time in which animals spent near conspecifics and increase the time close to the opponent image, suggesting a modulatory role in the approach/avoidance response. The treatment with carbetocin, an oxytocin receptor agonist, reestablished the behavioral phenotypes altered by MK-801 in both tests (Zimmermann et al., 2016). In sum, these results suggest that the exposure to MK-801 is highly attractive for assessing behavioral deficits and can serve as an interesting model for screening potential neuroprotectants. Considering the evolutionarily conserved actions of MK-801 in zebrafish, this species can be a suitable vertebrate to perform pharmacology investigations in medium-to-high-throughput screening protocols. Due to its antagonism of glutamatergic signaling, taurine appears as a candidate molecule to counteract the neurochemical and behavioral actions of MK-801 and other antiglutamatergic drugs in zebrafish, as well as testing potential antiglutamatergic effects of taurine.

6. Taurine and stress-related disorders

A biological hallmark of the stress response is the activation of the hypothalamic pituitary-adrenal (HPA) axis, triggering a “fight or flight” response with enhanced activation of the sympathetic nervous system when facing a dangerous situation, such as a predator, an accident, or a natural disaster (McEwen, 2007; Li and Hu, 2016). In teleost fish, cortisol is released from interrenal cells (adrenal gland homolog) during stress following activation of the hypothalamus–pituitary–interrenal (HPI) axis (Alsop and Vijayan, 2008; Alderman and Vijayan, 2012; Baiamonte et al., 2015). Various stressors rapidly increase whole-body cortisol in zebrafish reaching significant levels after 15 min (Barcellos et al., 2007; Barcellos et al., 2016; Ramsay et al., 2009).

Although stress response is adaptive, an excessive adrenocortical and autonomic function is harmful to health and survival. Dysregulation of HPA axis is associated with some psychiatric disorders (e.g. depression, posttraumatic stress disorder, anxiety) (Newport and Nemeroff, 2003; Holsboer, 2000; Walker et al., 2013; Moreno-Peral et al., 2014) and other biomedical conditions, including Type II diabetes, hypertension, chronic fatigue syndrome and fibromyalgia (Bruehl et al., 2007; Wirtz et al., 2007; Wingenfeld et al., 2008; Galli et al., 2009).

Although the influence of taurine in the neurobiology of stress is still poorly understood, TauT can be affected by distinct extracellular stimuli. For example, murine monocytic cell line RAW264.7 treated with 12-O-tetradecanoylphorbol 13-acetate (TPA) showed a marked reduction in TauT activity, which was reversed by steroid hormones (Kim et al., 1998). In a rat stress-induced hypertension model, animals treated with 200 mg/kg/day taurine and stressed for 3 weeks contained more angiotensin converting enzyme 2 (ACE2) than non-stressed and stressed groups (Lv et al., 2015). These data implicate taurine in the regulation of the HPA axis and renin-angiotensin-aldosterone system in stress-induced hypertension. In a randomized double-blind clinical trial, patients orally treated for 21 days with 1998 mg/day of a taurine analog acamprosate, markedly reduced alcohol consumption (Hammarberg et al., 2009). Given the influence of HPA on craving responses (Kiefer et al., 2006), these findings highlight the importance of using different experimental models to assess the neurobiological actions of taurine.

The relationship of taurine levels with distinct behavioral tests following acute stress in zebrafish has been previously investigated. Mushtaq et al. (2014) submitted zebrafish to a netting stress for fifteen minutes and further exposed the animals to the open field and light-dark tests. The authors observed changes in the metabolome with a significant increase in taurine levels when exposed to the light-dark apparatus vs. open field, regardless of experimentally evoked stress. However, since both tests may naturally cause various levels of stress (Kysil et al., 2017), studies aiming to assess the behavioral effects of taurine *per se* are imperative. In this context, Mezzomo et al. (2016) demonstrated an anxiolytic-like effect of taurine in zebrafish, since it increases the time spent in lit area and shuttling in the scototaxis after acute exposure. These neurobehavioral data reinforce that anxyolitic effects of taurine depend on experimental task and, thus, future evaluation are needed to clarify whether taurine may display an anti-stress activity in the species.

7. Conclusions

In summary, we emphasize the importance of further validation of zebrafish models to investigate the beneficial effects of taurine in the brain, and their underlying molecular mechanisms. Modeling both adult and larvae zebrafish endophenotypes using automated video-tracking systems associated with the measurement of biochemical and molecular endpoints has a great relevance to understand the pleiotropic actions of taurine in vertebrates. Since zebrafish embryos are transparent and larvae models allow the use of multiple animals in a same battery test (Best and Alderton, 2008; Best et al., 2008; Creton, 2009), protocols that evaluate the pharmacokinetics and the central mechanisms of taurine during development could be refined. Adult specimens display a wider spectrum of quantifiable behavioral phenotypes and well-developed motor, sensory and endocrine systems susceptible to environmental challenges (Burne et al., 2011; Cachat et al., 2010; Egan et al., 2009; Grossman et al., 2010; Norton and Bally-Cuif, 2010; Webb et al., 2009; Stewart et al., 2010, 2011a, 2011b). As shown in Table 2, although both adult and larval zebrafish models present some methodological limitations, they are particularly well suited for assessing the effects of taurine at behavioral and molecular levels in different experimental models of brain-related disorders. Thus, the use of zebrafish fosters translational neuroscience studies and *in vivo* pharmacological screening of taurine action in the CNS.

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Table 2
Potential beneficial effects of Tau as an additional treatment for brain disorders and the use of zebrafish with their limitations in translational neuroscience.

Brain disorders	Phenotypes	Strategy for treatment	Potential Tau actions	Translational validity of the zebrafish model	Protocol limitations
Alzheimer's disease	Deterioration of the cognitive functions with "fibers" and "small military" foci.	Use of cognitive enhancers to improve memory (e.g. donezepil, rivastigmine tartrate, galantamine HBr, memantine, and the psychostimulant modafinil).	Tau prevents the neurotoxicity of Aβ and via activation of $GABA_A$ receptors.	The neuronal structure possesses typical features observed in mammals.	Most of the models do not properly show evidence of significant permanent neuronal loss, a characteristic observed in age-related neurodegenerative disorders
	Deposition of a 39–43 amino acid residue peptide, known as Aβ, in the brain		Tau increases the survival of newborn neurons, resulting in a significant increase of neurogenesis.	High degree of physiological conservation regarding the mechanisms of action of different neurotransmitters.	
Parkinson's disease	Degenerative loss of dopaminergic nigrostriatal neurons.	Levodopa (L-dopa), a dopamine precursor, has a good therapeutic response.	Neuroprotective effect against glutamatergic excitotoxicity (probably unrelated with the blockade of glutamate receptors).	Extensive genomic information available on AD and PD-related genes of zebrafish.	
	Presence of intracytoplasmic LBs and intra-axonal LNs.		Neuromodulator in the nigrostriatal system.	Markedly behavioral changes (e.g. changes in locomotion and modification in anxiety-like behavior).	
Epilepsy	Sudden and abnormal discharges of neurons that may cause irreversible damage in the brain or even lead to death when not properly treated.	Conventional anti-epileptic drugs (AED) that exert their effects by inhibiting the sodium currents or by enhancing GABAergic inhibition.	Tau appears to modulate the neurotransmission by causing hyperpolarization and by inhibiting the firing of neurons.	Manifestation of tonic-clonic seizures as observed using EEG recordings in adult and larvae.	Drugs like PTZ and kainic acid induce similar seizure-like behaviors, but do not share the same mechanisms to induce seizures. Since there are no data regarding EEG recordings in kainic acid model, more studies are necessary to improve construct validity of the model.
Schizophrenia	Disturbance of dopamine metabolism, but the mechanisms of this disease are still unclear.	Antipsychotic drugs, chlorpromazine, a "phenothiazine antipsychotic" and "dopamine inhibitor".	Changes in Tau and GSH metabolism can be involved in the pathophysiology of the SCZ. These substances are important regulators of the redox balance and modulate inflammatory responses.	Genetic mechanisms mediating the neurogenesis of the dopaminergic system are well conserved between zebrafish and mammalian.	There are few animal models available to study behavioral and cognitive deficits and possible pharmacological interventions so far.
		Antagonists of serotonin 2A receptor ($5HT_{2A}$), which decreases extrapyramidal effects.	Tau may antagonize glutamatergic effects and counteract NMDA receptor activation.	Changes in locomotion, anxiety-like behavior, memory and social behavior have been described for zebrafish.	
Stress-related disorders	Activation of the HPA/HPI axis, triggering a "fight or flight" response with enhanced activation of the sympathetic nervous system.	Anxiolytic and antidepressant drugs (e.g. fluoxetine and buspirone inhibits stress-related changes).	Tau can regulate HPA axis and alter renin-angiotensin-aldosterone system playing a role in preventing stress-induced hypertension. Tau has anxiolytic-like effects in zebrafish. Tau could serve as an alternative treatment since it is an organic osmolyte able to regulate cell volume.	Similar to humans, cortisol is the main stress hormone in zebrafish, making it an attractive model organism for assessing the behavioral, neurochemical, physiological, and epigenetic effects of stressors. Extensive genomic information available on stress-related response genes of zebrafish during ontogeny.	Although the measurement of whole body cortisol is consistent with stress response, measuring circulating cortisol in larvae and adult specimens is difficult.

Abbreviations: Tau = Taurine; Aβ = amyloid beta; LBs = Lewy bodies; LNs = Lewy neurites; AD = Alzheimer's disease; PD = Parkinson's disease; EEG = electroencephalogram; PTZ = pentylenetetrazole; GSH = glutathione; SCZ = Schizoprenia; NMDA = N-methyl-D-aspartate; HPA = hypothalamic pituitary-adrenal axis; HPI = hypothalamus–pituitary–interrenal axis.

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5.2 ARTIGO 2

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The role of taurine on anxiety-like behaviors in zebrafish: A comparative study using the novel tank and the light-dark tasks.

Nathana J. Mezzomo, Ariane Silveira, Giulie S. Giuliani, Vanessa A. Quadros, Denis B. Rosemberg

Abstract

Taurine (TAU) is an amino sulfonic acid with several functions in central nervous system. Mounting evidence suggests that it acts in osmoregulation, neuromodulation and also as an inhibitory neurotransmitter. However, the effects of TAU on behavioral functions, especially on anxiety-related parameters, are limited. The adult zebrafish is a suitable model organism to examine anxiety-like behaviors since it presents neurotransmitter systems and behavioral functions evolutionary conserved. Anxiety in zebrafish can be measured by different tasks, analyzing the habituation to novelty, as well as the response to brightly lit environments. The aim of this study was to investigate whether acute TAU treatment alters anxiety-like behavior in zebrafish using the novel tank and the light-dark tests. Fish were individually treated with TAU (42, 150, and 400mg/L) for 1h and the behaviors were further analyzed for 6min in the novel tank or in the light-dark test. Control fish were handled in a similar manner, but kept only in home tank water. Although TAU did not alter locomotor and vertical activities, all concentrations significantly increased shuttling and time spent in lit compartment. Moreover, TAU 150 group showed a significant decrease in the number of risk assessment episodes. Overall, these data suggest that TAU exerts an anxiolytic-like effect in zebrafish and the comparative analysis of behavior using different tasks is an interesting strategy for neuropsychiatric studies related to anxiety in this species.

KEYWORDS: Anxiety; Defensive behaviors; Light–dark test; Novel tank; Taurine; Zebrafish

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Research paper

The role of taurine on anxiety-like behaviors in zebrafish: A comparative study using the novel tank and the light–dark tasks

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HIGHLIGHTS

- The effects of taurine were evaluated in zebrafish using two behavioral tasks.
- Taurine did alter neither locomotor activity nor vertical exploration.
- Taurine had anxiolytic-like effects in the light–dark test.
- Behavioral endpoints are differently altered by acute taurine treatment.

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ABSTRACT

Taurine (TAU) is an amino sulfonic acid with several functions in central nervous system. Mounting evidence suggests that it acts in osmoregulation, neuromodulation and also as an inhibitory neurotransmitter. However, the effects of TAU on behavioral functions, especially on anxiety-related parameters, are limited. The adult zebrafish is a suitable model organism to examine anxiety-like behaviors since it presents neurotransmitter systems and behavioral functions evolutionary conserved. Anxiety in zebrafish can be measured by different tasks, analyzing the habituation to novelty, as well as the response to brightly lit environments. The aim of this study was to investigate whether acute TAU treatment alters anxiety-like behavior in zebrafish using the novel tank and the light-dark tests. Fish were individually treated with TAU (42, 150, and 400 mg/L) for 1 h and the behaviors were further analyzed for 6 min in the novel tank or in the light–dark test. Control fish were handled in a similar manner, but kept only in home tank water. Although TAU did not alter locomotor and vertical activities, all concentrations significantly increased shuttling and time spent in lit compartment. Moreover, TAU 150 group showed a significant decrease in the number of risk assessment episodes. Overall, these data suggest that TAU exerts an anxiolytic-like effect in zebrafish and the comparative analysis of behavior using different tasks is an interesting strategy for neuropsychiatric studies related to anxiety in this species.

1. Introduction

Zebrafish (*Danio rerio*) is a small vertebrate model that has been considered a promising tool for the advancement of neuroscience and behavioral researches [1,2]. Several features like the presence of evolutionary conserved genes, sensitivity to pharmacological compounds, easy maintenance and low cost, have stimulated the use of zebrafish to model human diseases in a medium/large scale manner [3]. Additionally, different pharmacological agents that modulate synaptic transmission and neural membrane stability in humans show analogous activities in zebrafish, suggesting the existence of similar neural networks [4]. In this context, the use of zebrafish as an animal model to study defensive behaviors and anxiety-like parameters has increased considerably over the past few years [5–7].

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The behavior of rodents in response to anxiety has been extensively documented, but research with zebrafish is still limited [8]. Anxiety-like behavior is a complex phenotype evoked by dangerous or potentially dangerous environment/stimuli. It includes reduced exploration and typically manifests as geotaxis (diving), thigmotaxis, scototaxis, increased freezing, opercular movements, and erratic movements. Anxiolytic drugs generally reduce anxiety-like behaviors, while anxiogenic agents potentiate these responses [1,9]. In the literature, several neural mechanisms have been associated with anxiety-like behaviors (*e.g.*, modulation of $GABA_A$ receptors, strychnine-sensitive glycine receptors, and NMDA receptors) [10–12].

In the central nervous system (CNS), taurine (TAU) (2-aminoethanesulfonic acid) is a simple amino sulfonic acid which is not incorporated into proteins [13,14]. Its biosynthesis is dependent on sequential oxidative steps of cysteine, catalyzed by cysteine dioxygenase and cysteine sulfinate decarboxylase [15,16]. After glutamate, TAU is the second most abundant molecule in CNS [17] and plays multiple roles, including osmoregulation, neuroprotection, neuromodulation and inhibitory neurotransmission [18–20]. Previous reports showed that TAU acts as a ligand that activates $GABA_A$ and strychnine-sensitive glycine receptors [12]. Recent evidence also pointed a role of TAU as an activator of putative TAU receptors as well as an inhibitory molecule of the NMDA receptor complex through multiple mechanisms [10]. Since TAU interacts with GABAergic, glycinergic and glutamatergic receptors, it is a promising therapeutic tool for the treatment of anxiety-related disorders [21].

Recent studies have proposed the use of different protocols to measure anxiety-like behavior in zebrafish. The novel tank diving test is based on the natural instinct of zebrafish to initially seek protection in an unfamiliar environment avoiding the surface ('diving response') [22]. This test was introduced by Levin et al [23], who reported that adult zebrafish spent about 50% of a 5-min session in the bottom of a novel tank and showed that nicotine decreases this preference. Anxiolytic (anxiety-reducing) drugs, such as buspirone, diazepam and (chronic) fluoxetine, also decrease it, as well as the panicolytic agents (panic-reducing) [9,24]. A second task that evaluates anxiety-like behaviors is the light–dark test, which was proposed by Serra et al. [25]. and further validated by Maximino et al [26]. Zebrafish have a natural preference to dark (scototaxis) and such behavior is also modulated by pharmacological manipulations. Considering that different factors affect animal behavior, it is important to perform an integrated analysis of various anxiety-like parameters [8]. The comparison of the results obtained in multiple behavior tests can improve the knowledge of the variables modulated in the presence of different molecules. Thus, we aimed to investigate whether acute TAU treatment alters anxiety-like behavior of zebrafish using the novel tank and the light–dark tasks.

2. Materials and methods

2.1. Animals

Zebrafish (*Danio rerio*) were obtained from a local distributor (Hobby Aquarios, RS, Brazil). The animals used were approximately 50:50 male:female ratio of heterogeneous wild-type stock (short fin phenotype). Fish were acclimatized for 2 weeks in 40-L tanks filled with non-chlorinated water (at a maximum density of 2-3 animals per liter) under constant filtration and aeration before onset of experiments. The water temperature was set at $26 \pm 2\,^{\circ}C$, with pH adjusted to 7.0–7.5. The room illumination was provided by ceiling-mounted fluorescent light tubes and adjusted to a 14:10 light–dark photoperiod cycle (lights on at 7:00 am). The animals were fed thrice daily with a commercial fish flake food (Alcon Basic®, Alcon, Brazil) and maintained in accordance to the National Institute of Health Guide for Care and Use of Laboratory Animals. All protocols of this study were approved by the Ethics Commission on Animal Use of the Federal University of Santa Maria under process number 026/2014.

2.2. Treatments

To evaluate the role of taurine (Sigma, St. Louis, MO, USA) on anxiety-like behavior, we exposed the zebrafish individually for 1 h in 500-mL beakers at distinct TAU concentrations (42, 150, and 400 mg/L), named as TAU 42, TAU 150, and TAU 400, respectively. These concentrations has been extensively used in previous studies from our group which assessed neurochemical effects of TAU in zebrafish [16,27]. Additionally, this range (varying from 0.33 to 3.2 mM) is commonly used for *in vitro* and *in vivo* assays [18,28]. Control group was kept for 1 h under the same conditions, except that no TAU was added in the home tank water. A total of 80 fish were used for the experiments.

2.3. Behavioral tasks

The behavioral tests were performed during the same time frame each day (between 11:00 am and 4:00 pm) immediately after the treatments. All experiments were recorded using a webcam (Vtrex X6000®) in order to register the location and swimming activity of the zebrafish and analyzed by three trained observers (inter-rater reliability >0.85). The behavioral activity of zebrafish was recorded in a single session of 6 min and the behaviors were assessed using appropriate video-tracking software (ANY-maze®, Stoelting CO., USA) at a rate of 30 frames/s. Importantly, each animal was tested in a single apparatus (novel tank or light–dark task) to avoid possible stress promoted by subsequent manipulation and experiments. Thus, different cohorts were used for both experiments. All apparatuses were filled with water adjusted to home tank conditions and the experiments were performed on a stable surface with all environmental distractions kept to a minimum. The tank water was changed after each trial.

2.3.1. Novel tank diving test

The apparatus was consisted in a rectangular tank (25 cm length × 15 cm height × 6 cm width) filled with 1.5 L of home tank water. The aquarium was divided into three equal horizontal areas (bottom, middle, and top) and all experimental conditions were similar to those previously described [9,16,29]. The following endpoints were measured: total distance travelled, absolute turn angle, number of immobile episodes, latency to enter the top, time spent in top, and transitions to top area. For the novel tank diving test, a total of 48 fish were used ($n = 12$ per group).

2.3.2. Light–dark test

The light–dark test was performed based in the protocol described previously [26]. A rectangular glass tank (30 cm length × 10 cm width × 15 cm height) was divided into two equally sized partitions using black or white self-adhesive film externally covering the walls, floor, and the corresponding sides of the tank. Illumination was provided by fluorescent lamps at the ceiling (approximately 250 lux above the tank) and the apparatus was filled with 2.5 L of home tank water. After the treatments, fish were removed from the beakers and gently placed in the white partition of the tank. The trial was immediately started and behaviors were recorded in a single 6-min session. The following endpoints were automatically determined: time spent in lit area, shuttling, latency to enter the dark area, and number of risk assessment episodes. According to the literature, risk assessment is defined as a fast (>1 s) entry in the white compartment followed by re-entry

in the black compartment, or as a partial entry in the lit area [32]. The respective endpoint was measured manually by three trained researchers blind to the experiment (inter-rater reliability >0.85). The light/dark test was performed using a total of 32 fish ($n = 8$ per group).

2.4. Integrated biomarker response (IBR)

The "Integrated Biomarker Response" (IBR) was estimated based in log transformation to reduce variance and represented as star plots [30]. Data were log-transformed (Y_i) and the overall mean (μ) and standard deviation (s) were calculated. The Y_i values were further standardized by the formula: $Z_i = \left(\frac{Y_i - \mu}{s}\right)$ and the difference between Z_i and Z_0 (control) was calculated in order to determine A values. The IBR was assessed for each treatment by the sum of A values. The results were shown as star plot charts, representing the deviation of all behavioral endpoints in comparison to control (0).

2.5. Statistical analysis

The normal distribution of data and homogeneity of variances were checked by Kolmogorov–Smirnov and Bartlett's tests, respectively. In general, results were expressed as means ± standarderror of mean (S.E.M) and analyzed by one-way analysis of variance (ANOVA) followed by Student–Newman–Keuls multiple comparisons test. Given the asymmetric data distribution, the results of immobility and latencies to enter the top/dark areas were expressed as median ± interquartile range. Statistical analysis was carried out with the Kruskal–Wallis test (considering treatment as the independent variable), followed by the Dunn's *post hoc* test. All experiments were performed using $n = 8$–12 per group. Results were considered significant at a $P \leq 0.05$ level.

3. Results

Firstly, we analyzed the effects of acute TAU treatments in the novel tank test. The total distance travelled, absolute turn angle, and also the number of immobile episodes of TAU-treated animals were similar to the control group ($P > 0.05$) (Fig. 1A). Moreover, TAU did not promote significant changes on the vertical exploratory activity of zebrafish, as observed in the latency to enter the top, time spent in the upper area and in the number of transitions to top ($P > 0.05$) (Fig. 1B).

Conversely, TAU-treated fish presented substantial differences in the light–dark test when compared to untreated animals (Fig. 2). One way ANOVA followed by Student–Neuman–Keuls test revealed that TAU, at all concentrations tested, significantly increased the time spent in the lit area (F [3,29] = 4.046, $P = 0.0161$) and shuttling (F [3,29] = 3.661, $P = 0.0237$). In addition, the results showed that TAU 150 group presented a decrease in risk assessment episodes (F [3,29] = 3.691, $P = 0.0230$). The average duration of entry in lit area as well as the latency to enter the dark area did not significantly differ among the experimental groups. These results were further corroborated by IBR plots, which showed that the behavioral endpoints of zebrafish measured in both tasks are differently altered by TAU concentrations (Fig. 3).

4. Discussion

In this study, we performed a comparative analysis to investigate whether TAU plays a role on anxiety-like behaviors of zebrafish in both novel tank and light–dark tasks. In the novel tank test, TAU did affect neither locomotion nor vertical exploration. However, in the light-dark apparatus, TAU-treated fish spent more time in the lit area and increased the number of crossings. To our knowledge, these data represent the first evidence suggesting that acute TAU treatment decreases anxiety-like behavior in zebrafish.

Defensive behaviors constitute a wide range of innate strategies involved in seeking protection against possible threats [34]. The risk assessment is a behavioral endpoint related to defensive approach which consists in a careful investigation of potentially aversive environments [1,32]. We observed that TAU 150 showed decreased risk assessment episodes when compared to the other experimental groups, suggesting an effect on anxiety-like behavior and defensive approach. Furthermore, TAU selectively produces the strongest effects on different behaviors in a concentration-dependent manner (time in lit area at TAU 400, shuttling at TAU 42, and risk assessment at TAU 150). These results may be supported by the higher sum of A values obtained using IBR analysis of behavioral endpoints, displaying a distinct response of TAU in the novel tank and light–dark tests. The existence of different responses triggered by TAU in zebrafish is not surprising. Previous studies from our group showed that acute TAU treatment exerts a biphasic effect on aggressive behavior of zebrafish. Exposure to 42 and 400 mg/L TAU enhance aggression without altering locomotor and motor patterns, while this effect is absent in 150 mg/L TAU [35]. Although these same concentrations prevent locomotor impairments triggered by ethanol in zebrafish, a biphasic response in vertical exploration is also observed when TAU is previously administered in an acute ethanol exposure model [16]. These data strongly support the idea that, similarly to what occur in mammalian models, TAU modulates aggression and exerts a neuroprotective action in teleosts. Kozlowski et al. [36]. demonstrated that high levels of taurine transporter (TauT), which is highly homologous to its mammalian counterpart, are expressed in whole brain during zebrafish development, suggesting a conserved role of TAU among vertebrates. At this moment, we do not have a clear explanation about the underlying mechanisms of TAU in zebrafish brain. However, taking into consideration that TAU plays several roles to maintain brain homeostasis [10–12,18,19], our data support the existence of different mechanisms of action of TAU on motivational aspects related to anxiety-like behaviors.

Anxiolytic drugs generally reduce anxiety-like behaviors [1,9] and the use of distinct tasks is an interesting approach to understand how behavioral phenotypes are modulated by such compounds. The novel tank test is a useful method to assess the consequences of stressful manipulations in zebrafish [8]. Fish have a natural tendency to initially dive to the bottom of a novel environment and then gradually explore the higher portions of the test tank [23,29], suggesting that the novel tank may reflect habituation to novelty stress [31]. Studies showed that nicotine and other anxiolytic compounds, like buspirone, diazepam and fluoxetine may decrease bottom-dwelling. A similar effect was also observed after exposure to the tranylcypromine, a panicolytic drug [9,24]. On the other hand, the light–dark test has been considered more specific to assess anxiety-like behaviors in zebrafish. Pharmacological evidence showed that, differently to what occurs in the novel tank, the behaviors measured in the respective task are sensitive to anxiolytic, but not panicolytic drugs and do not present intra or intersession habituation [32]. Considering that surface avoidance is the main behavior assessed by the novel tank test, while aversion to brightly lit environments is related to the light–dark test, distinct constructs are probably measured in both tasks [8,29,33]. Our data demonstrate that TAU per se does not alter vertical exploration, but it increases the shuttling and the time spent in lit area. Since the novel tank and light–dark tests may not assess the same motivational state, we suggest that anxiolytic-like effects of TAU could involve neurochemical signaling pathways associated to scototaxis, but unrelated to bottom dwelling response.

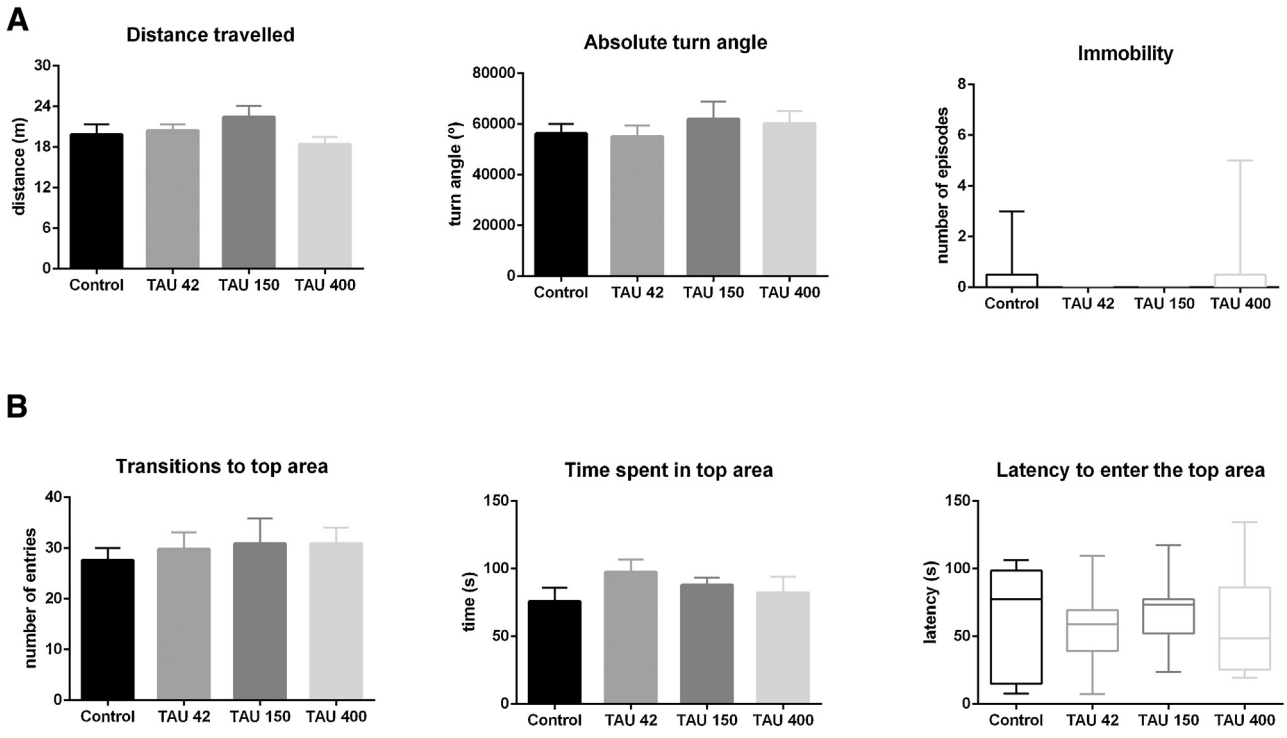

Fig. 1. Effects of acute TAU treatment in the novel tank diving test. The figure shows both locomotor parameters (panel A) and vertical exploratory activity (panel B). Data were expressed as means ± S.E.M and analyzed by one-way ANOVA, except the immobility and the latency to enter the top, which were expressed as median ± interquartile range and analyzed by Kruskal–Wallis test. The experiments were performed using $n = 12$ per group.

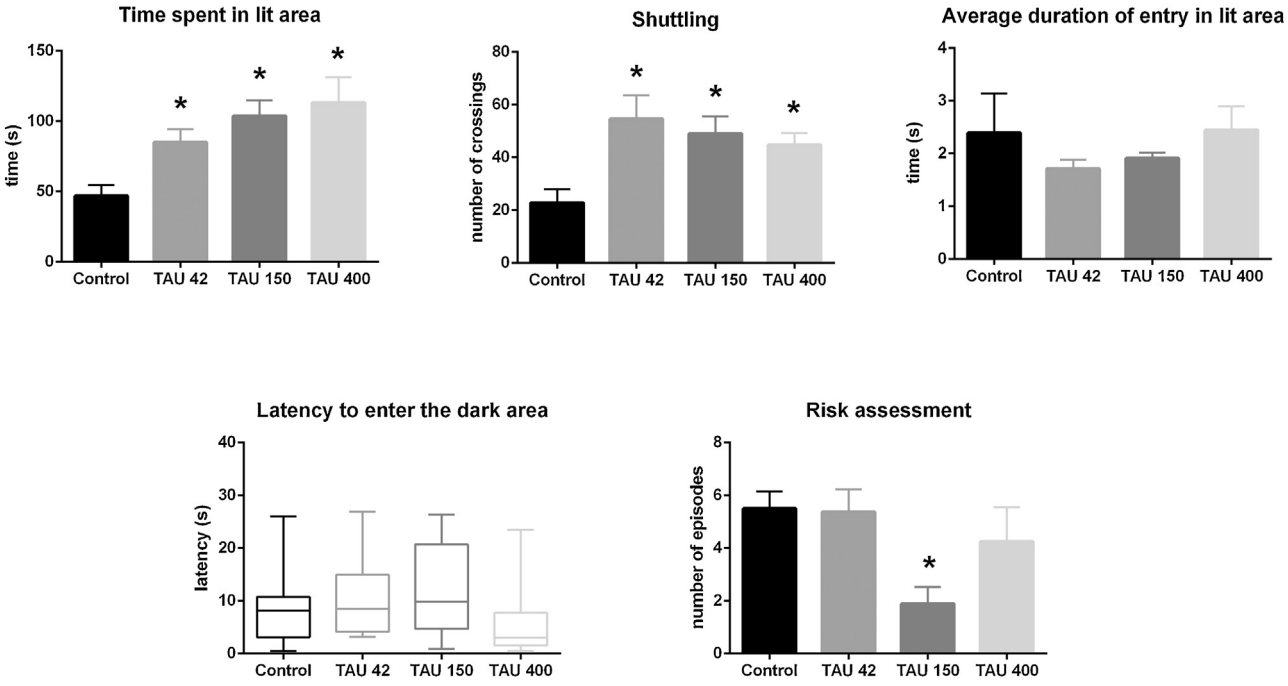

Fig. 2. Different actions of TAU in the scototaxis test. The figure demonstrates the effects of 42, 150, and 400 mg/L TAU on anxiety-like behaviors. Data were expressed as means ± S.E.M and analyzed by one-way ANOVA, followed by the Student–Neuman–Keuls *post hoc* test (time spent in lit area, shuttling, risk assessment episodes). Results of the latency to enter the dark area were expressed as median ± interquartile range and analyzed by Kruskal–Wallis test. The asterisks represent statistical differences as compared to control ($P \leq 0.05$, $n = 8$ per group).

5. Conclusions

In summary, we reported that acute TAU treatment did alter neither locomotor nor vertical activities in zebrafish. Considering that the animals spent more time in the lit area and increased the number of crossings between both compartments in the light-dark test, an anxiolytic-like effect of TAU is predicted. Despite the anxiolytic-like effects observed in the current report, more studies are necessary to clarify the mechanisms of action of TAU in zebrafish CNS. This fact can be sustained by our comparative study since the

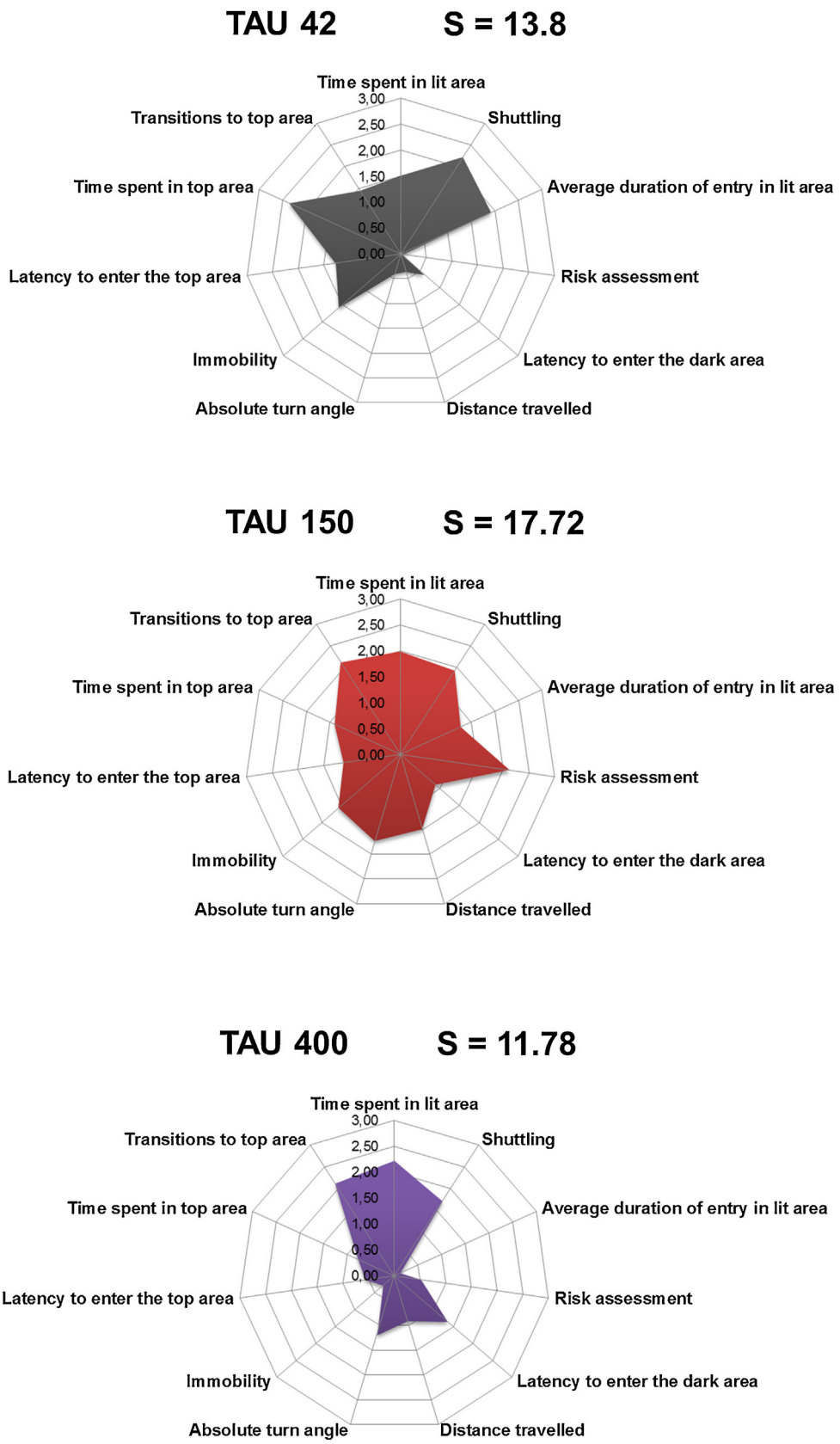

Fig. 3. IBR plots showing the effects of TAU in behavioral endpoints. The main behaviors of zebrafish in the novel tank and light dark tests are depicted as IBR star plot graphs for each TAU concentration (42, 150, and 400 mg/L).

novel tank and light–dark tests trigger distinct stimuli that generate a conflict between exploration to novelty and light avoidance.

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5.3 ARTIGO 3

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Taurine modulates the stress response in zebrafish.

Nathana J. Mezzomo, Barbara D. Fontana, Talise E. Müller, Tâmie Duarte, Vanessa A. Quadros, Julia Canzian, Aline Pompermaier, Suelen M. Soares, Gessi Koakoski, Vania Loro, Denis B. Rosemberg, Leonardo J. G. Barcellos

Abstract

The zebrafish (*Danio rerio*) is used as an emergent model organism to investigate the behavioral and physiological responses to stress. The anxiolytic-like effects of taurine in zebrafish support the existence of different mechanisms of action, which can play a role in preventing stress-related disorders (i.e., modulation of $GABA_A$, strychnine-sensitive glycine, and NMDA receptors, as well as antioxidant properties). Herein, we investigate whether taurine modulates some behavioral and biochemical responses in zebrafish acutely submitted to chemical and mechanical stressors. We pretreated zebrafish for 1 h in beakers at 42, 150, and 400 mg/L taurine. Fish were later acutely exposed to a chemical stressor (conspecific alarm substance) or to a mechanical stressor (net chasing), which elicits escaping responses and aversive behaviors. Locomotion, exploration, and defensive-like behaviors were measured using the novel tank and the light-dark tests. Biochemical (brain oxidative stress-related parameters) and whole-body cortisol levels were also quantified. We showed that taurine prevents anxiety/fear-like behaviors and protein carbonylation and dampens the cortisol response following acute stress in zebrafish. In summary, our results demonstrate a protective role of taurine against stress-induced behavioral and biochemical changes, thereby reinforcing the growing utility of zebrafish models to investigate the neuroprotective actions of taurine in vertebrates.

KEYWORDS: Antioxidant Enzymes; Anxiety/Fear-like Behaviors; Cortisol; Neuroprotection.

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Taurine modulates the stress response in zebrafish

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ABSTRACT

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1. Introduction

The zebrafish (*Danio rerio*) is widely used as a model organism to investigate behavioral and neurochemical aspects of stress-related neuropsychiatric disorders (Brennan, 2011; Fontana et al., 2019; Kalueff et al., 2014; Mezzomo et al., 2018; Norton and Bally-Cuif, 2010; Norton, 2013). This species shows a high degree of genetic and physiological conservation, with various brain structures having homologous functions when compared with the mammalian counterparts (Randlett et al., 2015; Ullmann et al., 2010). The lateral pallium of the telencephalon is responsible for memory processing, while the dorsal habenula controls anxiety/fear responses (Mathuru and Jesuthasan, 2013). These brain structures are analogous to the hippocampus and amygdala, respectively (Agetsuma et al., 2010; Perathoner et al., 2016). Moreover, the zebrafish expresses all major neurotransmitter systems (*e.g.*, dopaminergic, serotonergic, cholinergic, and noradrenergic) described in mammals (Agostini et al., 2018; Kastenhuber et al., 2010; Lillesaar et al., 2007; Schweitzer and Driever, 2009). Zebrafish displays complex cognitive processing and decision-making strategies, showing high sensitivity to pharmacological agents that modulate behavioral functions (Oliveira, 2013; Parker et al., 2012; Sison et al., 2006). This species shows robust aversive responses (*e.g.*, anxiety/fear-like behaviors), when exposed to stressors, which are pharmacologically sensitive to antistress agents (Gerlai, 2010; Maximino et al., 2010; Steenbergen et al., 2011). When studying anxiety/fear responses resulting from abnormal stress-related physiology, stress hormone levels and oxidative stress-related parameters can serve as valuable tools to parallel with behavioral observations (Alsop and Vijayan, 2009; Holsboer, 2000; Moreno-Peral et al., 2014; Newport and Nemeroff, 2000; Walker et al., 2013).

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The hypothalamic–pituitary–interrenal (HPI) axis coordinates the stress responses in zebrafish, which involves a cascade of hormones, starting from corticotropin-releasing factor (CRF) to adrenocorticotropic hormone (ACTH) and cortisol, released from the interrenal cells (adrenal gland homolog) (Fuzzen et al., 2010; Ghisleni et al., 2012; Tran et al., 2014). Cortisol binds to the glucocorticoid receptor that regulates the transcription of target genes related to glucose metabolism, immune function, and behavior (Bury and Sturm, 2007; Vijayan et al., 2016). Numerous reports show the growing utility of zebrafish models for assessing behavioral, neurochemical, physiological, and epigenetic effects of stress (Barcellos et al., 2016; Barcellos et al., 2011; Koakoski et al., 2014; Nesan and Vijayan, 2016). Stress-related genes are expressed early in life, such as *crf*, proopiomelanocortin (*pomc*), melanocortin 2 receptor (*mc2r*), and steroidogenic acute regulatory protein (*star*) (Oltrabella et al., 2015), while stressor-induced cortisol responses occur after 97 hpf (Alsop and Vijayan, 2009). Thus, the zebrafish represents a useful animal model to investigate the molecular bases underlying human stress physiology (Alderman and Vijayan, 2012; Alsop and Vijayan, 2009; Baiamonte et al., 2015).

Stress represents a response to a stressful condition, such as a threat, challenge, or physical and psychological barrier (Selye, 1976; Ulrich-Lai et al., 2016), while fear and anxiety are primitive emotions to ensure safety when animals respond to challenge (Sylvers et al., 2011). In the clinical literature, fear is a cognitive response to an imminent threat, whereas anxiety is an emotional response to fear (Lang et al., 2000). Thus, failure to extinguish fear responses is a key contributing factor in anxiety- and stress-related disorders (Perathoner et al., 2016; Radulovic et al., 2018). The constructs of fear and anxiety are delineated more clearly in the neuroscience literature. While anxiety is triggered by potentially threatening situations, fear usually occurs in the presence of a real threat. Some stressors usually trigger higher levels of anxiety/fear-like behaviors in zebrafish. For example, both acute conspecific alarm substance (CAS) exposure and net chasing elicit escaping responses and aversive behaviors (Abreu et al., 2014; Barcellos et al., 2011; Cachat et al., 2010; Egan et al., 2009; Mathuru et al., 2012; Mocelin et al., 2015). CAS increases *c-fos* expression in habenula and causes prolonged defensive behaviors, hence characterizing a persistent fear-like response (Maximino et al., 2018; Ogawa et al., 2014; Ogawa et al., 2012). Conversely, net chasing robustly increases cortisol levels, which reflect a high-stress condition (Abreu et al., 2014; Barcellos et al., 2011; Mocelin et al., 2015). Because chemical and mechanical stressors are different in nature, pharmacological interventions aiming to prevent specific stress-induced phenotypes are important.

Taurine (2-aminoethanesulfonic acid) plays a pleiotropic role by modulating osmoregulation (Schaffer et al., 2010), membrane stability (Lambert et al., 2015), intracellular calcium metabolism (Foos and Wu, 2002), and neuronal activity (Wu and Prentice, 2010). Importantly, taurine prevents oxidative stress (Lerdweeraphon et al., 2013) and inflammation (Marcinkiewicz and Kontny, 2014) and hence acts as an endogenous neuroprotector (Menzie et al., 2014) by positively modulating $GABA_A$ and strychnine-sensitive glycine receptors and inhibiting NMDA receptor activation (Chan et al., 2014; Poleszak et al., 2011; Zhang and Kim, 2007). Because neuroprotective effects of taurine in zebrafish support the existence of different mechanisms of action (Fontana et al., 2016; Fontana et al., 2019; Mezzomo et al., 2016; Rosemberg et al., 2012; Rosemberg et al., 2010), herein, we investigated whether taurine prevents fear/anxiety-like behavioral, neurochemical, and physiological responses in zebrafish submitted to different stressors.

2. Materials and methods

2.1. Animals

Subjects were adult *short fin* zebrafish (*D. rerio*) (4–6 months old, ~50:50 male-to-female ratio, weighing 0.25–0.4 g) obtained from a local distributor (Hobby Aquários, Santa Maria, RS). Fish were acclimated in the laboratory for 15 days in 50 L tanks with a maximum density of 2 animals/L; the tanks contained nonchlorinated water kept under constant aeration and mechanical and chemical filtration at 25 ± 2 °C, pH = 7.1. The water conditions were monitored using commercial kits for determining pH, nitrite, and ammonia (Alcon Basic®, Alcon, Brazil). Fluorescent lamp tubes were used to provide illumination by adjusting to a 14/10 h light/dark photoperiod cycle (lights on at 7:00). Fish were fed twice daily with commercial flake food (Alcon Basic®, Alcon, Brazil) and maintained in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals. All experimental procedures were approved by the Ethics Committee on Animal Use of the Federal University of Santa Maria (protocol number 106/2014). Moreover, this research was registered in the SisGen (Sistema Nacional de Gestão do Patrimônio Genético e do Conhecimento Tradicional Associado) and complied with their guidelines (registration code A14E252).

2.2. Experimental design

Our study strategy was to compare behavioral and biochemical stress-related responses in zebrafish in the absence or presence of taurine. The experimental design consisted of exposing fish to water (control group) or taurine (taurine groups) before the induction of acute stress in another tank. Behavioral activities were further analyzed using the novel tank test or the light–dark test. Whole-body cortisol levels and biochemical assays were measured following the behavioral tests.

2.2.1. Taurine pretreatment

To evaluate the effects of taurine (Sigma, St. Louis, MO, USA) on acute stress, we exposed zebrafish individually for 1 h in 500 mL beakers at different taurine concentrations (42, 150, and 400 mg/L). Both exposure period and taurine concentrations were chosen on the basis of those reported in previous studies, which showed positive effects in zebrafish (Fontana et al., 2016; Fontana et al., 2019; Mezzomo et al., 2016; Rosemberg et al., 2012). The water (control) group was kept in nonchlorinated water for the same period. After transferring the fish individually to the behavioral apparatus, the videos were recorded for 6 min and later analyzed using ANY-Maze™ software (Stoelting Co., USA). All behavioral tests were performed between 09:00 and 11:00 AM. Brains were dissected immediately after the behavioral tasks for biochemical assays, and fish submitted to whole-body cortisol extraction were euthanized after 15 min. To ensure data reliability, two independent batches were tested (n = 5–7 per group in each batch).

2.2.2. Acute stress induction

After water or taurine exposure, the induction of stress was performed in another tank using two stressors of different natures. Subsequently, the behavior was analyzed in the novel tank test or in the light–dark test. One cohort of animals was submitted to a mechanical stressor (chasing fish with a net), while another cohort was exposed to a chemical stressor (acute CAS exposure). Mechanical stress was induced by chasing the fish with a net for 2 min as described elsewhere (Abreu et al., 2014; Barcellos et al., 2011; Mocelin et al., 2015). The same trained experimenter executed the net chasing stress protocol (circular clockwise movements with the net, at a regular speed of approximately 40 turns per minute). The protocol of chemical stress induction was performed as described previously (Canzian et al., 2017; Egan et al., 2009; Quadros et al., 2016; Speedie and Gerlai, 2008). CAS was extracted from phenotypically similar donor fish previously euthanized. Briefly, epidermal cells were damaged with 10–15 shallow slices on both sides of the donor fish body with a razor blade. All procedures were performed on ice and carefully controlled to avoid drawing blood, which would contaminate the solution. Afterward, 10 mL of distilled water was added into a Petri dish and gently shaken to fully cover the fish body. Animals were exposed individually to 3.5 mL/L CAS

preparation in 500 mL tanks for 5 min. Control groups were handled in a similar manner as that of the test groups, except that only distilled water was added to the tank.

2.3. Behavioral tests

2.3.1. Novel tank diving test

The apparatus was a glass aquarium (20 cm length × 20 cm height × 20 cm width) filled with 1.5 L of home tank water. The apparatus was divided into two equal horizontal areas (bottom and top), and all experimental conditions were similar to those described previously (Egan et al., 2009; Rosemberg et al., 2012; Rosemberg et al., 2011). The following endpoints were measured: time spent in the top area, transitions to the top area, and the number and duration of erratic movements. Erratic movements consist of fast and successive swimming bouts with abrupt changes in direction (Kalueff et al., 2013). Because automated video tracking systems do not precisely quantify some behaviors with the accuracy of human interpretation, erratic movements were manually computed by two observers blinded to the experimental condition (inter-rater reliability > 0.85).

2.3.2. Light–dark test

The light–dark test was performed according to the protocol described previously (Maximino et al., 2010). A rectangular glass tank (25 cm length × 10 cm width × 30 cm height) was divided into two equally sized partitions using a black and white self-adhesive film externally covering the walls, floor, and the corresponding sides of the tank. The apparatus was filled with 2.5 L of home tank water, and after the treatments, fish were removed from the beakers and gently placed in the test apparatus. All behaviors were recorded in a single 6 min session, and the following endpoints were quantified: time spent in the lit area, shuttling, transitions to the lit area, and number of risk assessment episodes. Risk assessment was defined as a fast (> 1 s) entry into the white compartment followed by re-entry into the black compartment, or as a partial entry in the lit area (Kalueff et al., 2013; Maximino et al., 2011). Risk assessment was measured manually by two trained observers blinded to the experimental condition (inter-rater reliability > 0.85).

2.4. Biochemical analyses

After behavioral tests, fish were euthanized, and the brains were immediately dissected on ice, transferred to microtubes, and stored at −80 °C. Three brains were pooled per sample and homogenized in 570 μL of 50 mM Tris-HCl buffer, pH 7.4. Samples were further centrifuged (3000 *rpm* for 10 min, −4 °C), and the supernatants were used for subsequent assays.

2.5. Oxidative stress-related parameters

Lipid peroxidation was estimated by thiobarbituric acid reactive substance (TBARS) production as described elsewhere (Draper and Hadley, 1990; Rosemberg et al., 2010). Samples (80 μg protein) were mixed with 10% TCA and further centrifuged at 10,000 × *g* for 10 min. Supernatants were further mixed with 0.67% thiobarbituric acid and boiled for 30 min. TBARS levels were determined at 532 nm using malondialdehyde (MDA) as standard. Results were expressed as nmol MDA/mg protein. Carbonylated protein (CP) levels were quantified by protein precipitation in the presence of trichloroacetic acid and dinitrophenylhydrazine (DNPH) (Fontana et al., 2019; Yan et al., 1995). Protein samples (200 μL) were mixed with 10 mM DNPH and incubated for 1 h in the dark. Later, 0.15 mL of denaturing buffer (150 mM sodium phosphate buffer, pH 6.8, containing SDS 3.0%), 0.5 mL of heptane (99.5%), and 0.5 mL of ethanol (99.8%) were added sequentially, kept in continuous agitation for 40 s, and centrifuged for 15 min at 1000 × *g*. The isolated protein was then washed twice by resuspension in ethanol/ethyl acetate (1:1) and suspended in 0.25 mL of denaturing buffer. CP content was measured spectrophotometrically at 370 nm in a microplate reader and expressed as nanomole carbonyl/milligram protein and calculated using the molar extinction coefficient (22.000 M/cm).

2.6. Determination of antioxidant enzymes

Superoxide dismutase (SOD) activity was assessed by measuring the adrenaline oxidation rate at 480 nm as described previously (Misra and Fridovich, 1972). The incubation medium contained glycine–NaOH buffer (50 mM, pH 10), adrenaline (1 mM), and homogenate (20–30 μg of protein). SOD activity was quantified in a microplate reader and expressed as unit SOD/milligram protein (Rosemberg et al., 2010). Catalase (CAT) activity was assessed by measuring the decrease in hydrogen peroxide absorbance at 240 nm by ultraviolet spectrophotometry (Aebi, 1984). The assay mixture had 1 mL potassium phosphate buffer (50 mM, pH 7.0), 0.05 mL H_2O_2 (0.3 M), and 0.01 mL homogenate (20–30 μg of protein). Results were expressed as U/milligram of protein (Rosemberg et al., 2010).

2.7. Protein quantification

Total protein amount was determined spectrophotometrically by the Coomassie blue method using bovine serum albumin as the standard at 595 nm (Bradford, 1976).

2.8. Cortisol extraction and analysis

Whole-body cortisol levels were used as an indicator of stress response. Fish were captured and immediately frozen in liquid nitrogen for 10–30 s, followed by storage at −20 °C until cortisol extraction. Whole-body cortisol was extracted according to the method described elsewhere (Oliveira et al., 2013). Fish were weighed, minced, and placed in a disposable stomacher bag with 2 mL phosphate buffered saline (PBS, pH 7.4) for 6 min. The contents were then transferred to a 10 mL screw top disposable test tube, to which 5 mL of laboratory-grade ethyl ether was added. The tube was vortexed for 1 min and centrifuged for 10 min at 3000 *rpm*, after which the sample was immediately frozen in liquid nitrogen. The unfrozen portion (ethyl ether containing cortisol) was decanted and transferred to a new tube and completely evaporated under a gentle stream of nitrogen for 2 h, yielding a lipid extract containing cortisol, which was stored at −20 °C. The accuracy was tested by calculating the recoveries from samples spiked with known amounts of cortisol (50, 25, and 12.5 ng/mL). The mean detection of spiked samples was 94.3%. All cortisol values were adjusted for recovery with the following equation: Cortisol value = Measured value x 1.0604. Tissue extracts were resuspended in 1 mL PBS, and whole-body cortisol levels were measured in duplicate for each extraction using a commercially available enzyme-linked immunosorbent assay kit (EIAgen™ Cortisol test, BioChem ImmunoSystems) (Sink et al., 2008). Precision was tested by performing 12 repeated assays on seven randomly chosen samples on the same 96-well plate and calculating the intra-assay coefficient of variation (CV). The reproducibility was assessed by testing the same samples on different plates and calculating the inter-assay CV. To test for linearity and parallelism, tissue samples were subjected to serial dilutions in the buffer provided with the kit. A strong positive correlation between the curves was observed (R^2 = 0.8918), and the samples yielded low inter- and intra-assay CV values (7–10% and 5–9%, respectively).

2.9. Statistical analysis

Normality of data and homogeneity of variances were analyzed by Kolmogorov–Smirnov and Bartlett's tests, respectively. Nonparametric data were log transformed and analyzed by two-way analysis of variance (ANOVA), considering treatment and stress as factors, followed

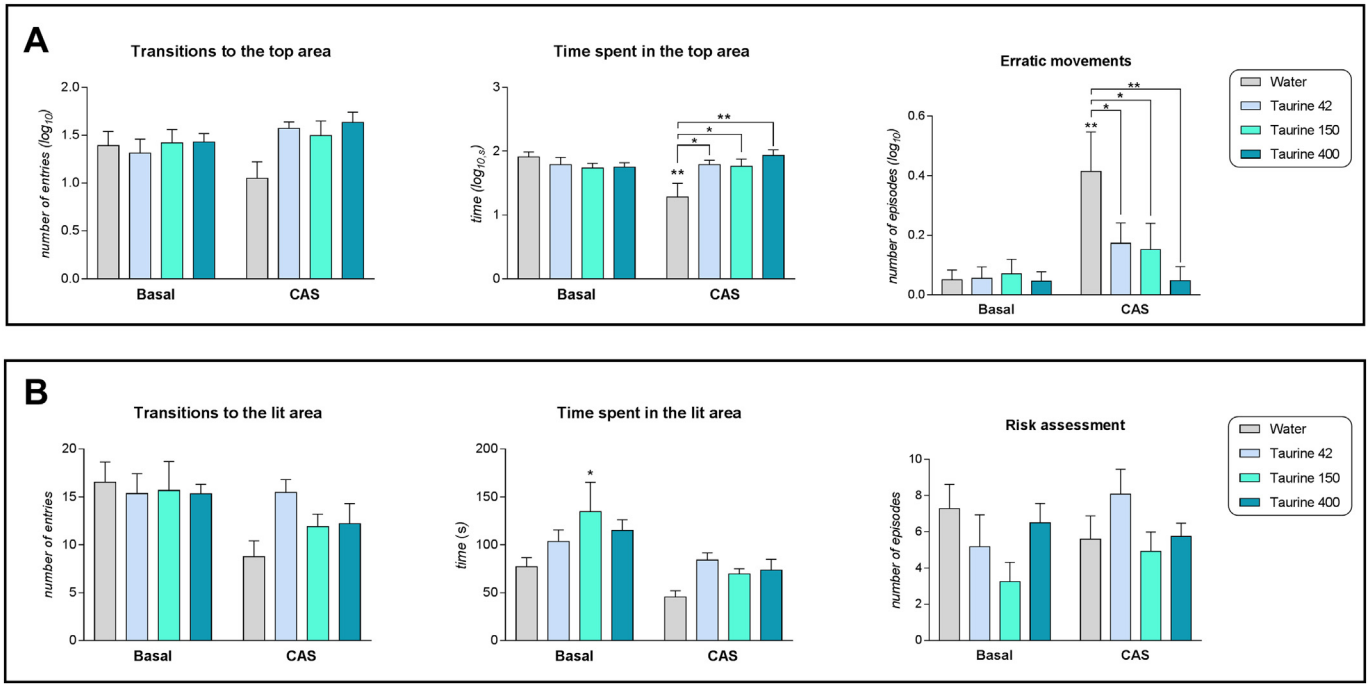

Fig. 1. Behavioral effects of taurine on CAS-induced chemical stress. (A) Novel tank diving test. (B) Light–dark test. Data were expressed as mean ± S.E.M and analyzed by two-way ANOVA, followed by the Student–Newman–Keuls multiple comparison test. Statistical significance was set at $P \leq 0.05$. Asterisks above bars express significant differences compared to the control group, while asterisks above brackets indicate statistical differences compared to the CAS group (n = 10–14 animals per group; CAS: conspecific alarm substance; *$P < 0.05$, **$P < 0.01$).

by Student–Newman–Keuls (SNK) multiple comparison test; results were expressed as mean ± standard error of mean (S.E.M). The level of significance was set at $P \leq 0.05$, and effect sizes were reported as generalized eta squared (gεs).

3. Results

3.1. Behavioral effects

3.1.1. Effects of taurine on CAS-induced chemical stress

Fig. 1A displays the behavioral effects of taurine on CAS-induced chemical stress in the novel tank test. A significant interaction was observed for time spent in the top area [$F_{3,85} = 5.10$, $P = 0.0027$, gεs = 0.14], and erratic movements [$F_{3,85} = 2.74$, $P = 0.0483$, gεs = 0.32]. Additionally, a CAS effect was observed for number of erratic movements [$F_{1,85} = 9.58$, $P = 0.0027$, gεs = 0.09]. CAS-induced chemical stress increased erratic movements and reduced of time spent in the top area, and all treatments abolished these effects.

Fig. 1B shows the behavioral effects of taurine on CAS-induced chemical stress in the light–dark test. Although no interaction effect CAS *vs.* treatment was observed for transitions to the lit area [$F_{3,89} = 1.33$, $P = 0.2686$, gεs = 0.03], or time spent to the lit area [$F_{3,85} = 1.17$, $P = 0.3265$, gεs = 0.02], a significant effect of the CAS was observed for time spent to the lit area [$F_{1,85} = 21.06$, $P = 0.0001$, gεs = 0.17], and transitions to the lit area [$F_{1,89} = 6.94$, $P = 0.0099$, gεs = 0.07]. Meanwhile, a treatment effect was observed for time spent to the lit area [$F_{3,85} = 4.34$, $P = 0.0068$, gεs = 0.11], where taurine 150 alone increased time spent to the lit area.

3.1.2. Effects of taurine on chasing-induced mechanical stress

Fig. 2 displays the behavioral effects of taurine on chasing-induced mechanical stress. A significant effect of interaction was observed for time spent in the top area [$F_{3,96} = 2.94$, $P = 0.0372$, gεs = 0.08] in the novel tank test (Fig. 2A). No significant effects were observed among treatments in the light–dark test (Fig. 2B).

3.2. Biochemical effects

3.2.1. Effects of taurine on CAS-induced chemical stress

Fig. 3A demonstrates the effects of taurine on CAS-induced chemical stress in oxidative stress-related parameters. A significant interaction was observed for carbonylated proteins levels [$F_{3,34} = 41.46$, $P < 0.0001$, gεs = 0.37], and lipid peroxidation [$F_{3,33} = 4.45$, $P = 0.0098$, gεs = 0.23]. As well, a CAS effect was detected for carbonylated proteins levels [$F_{1,34} = 111.5$, $P < 0.0001$, gεs = 0.33], and lipid peroxidation [$F_{1,33} = 4.37$, $P = 0.0442$, gεs = 0.07]. Moreover, a treatment effect was observed for carbonylated proteins levels [$F_{3,34} = 21.82$, $P < 0.0001$, gεs = 0.19]. CAS-induced carbonylated proteins levels, and this effect was potentiated in taurine 400 group subjected to stress.

The effects of taurine on antioxidant enzymes are displayed in the Fig. 3B, where an effect of interaction was observed [$F_{3,33} = 12.78$, $P < 0.0001$, gεs = 0.39], CAS effect [$F_{1,33} = 5.23$, $P = 0.0287$, gεs = 0.05], and treatment [$F_{3,33} = 7.29$, $P = 0.0007$, gεs = 0.22] for SOD activity. As a result, SOD activity was markedly potentiated in taurine 400 group subjected to CAS-induced stress. No significant effects were observed in CAT activity.

3.2.2. Effects of taurine on chasing-induced mechanical stress

Fig. 4A demonstrates the effects of taurine on chasing-induced mechanical stress in oxidative stress-related parameters. A significant interaction was observed for carbonylated proteins levels [$F_{3,32} = 34.89$, $P < 0.0001$, gεs = 0.30]. Additionally, a significant effect of NC was observed for carbonylated proteins levels [$F_{1,32} = 134.4$, $P < 0.0001$, gεs = 0.38], and lipid peroxidation [$F_{1,35} = 110.7$, $P < 0.0001$, gεs = 0.73]. Furthermore, a significant effect of treatment was observed for carbonylated proteins levels [$F_{3,32} = 26.86$, $P < 0.0001$, gεs = 0.23]. Chasing-induced stress induced lipid peroxidation and protein carbonylation. Taurine 42 prevented, and taurine 400 markedly potentiated protein carbonylation.

The effects of taurine on antioxidant enzymes are exhibited in the Fig. 4B. Although no interaction effect NC *vs.* treatment was revealed

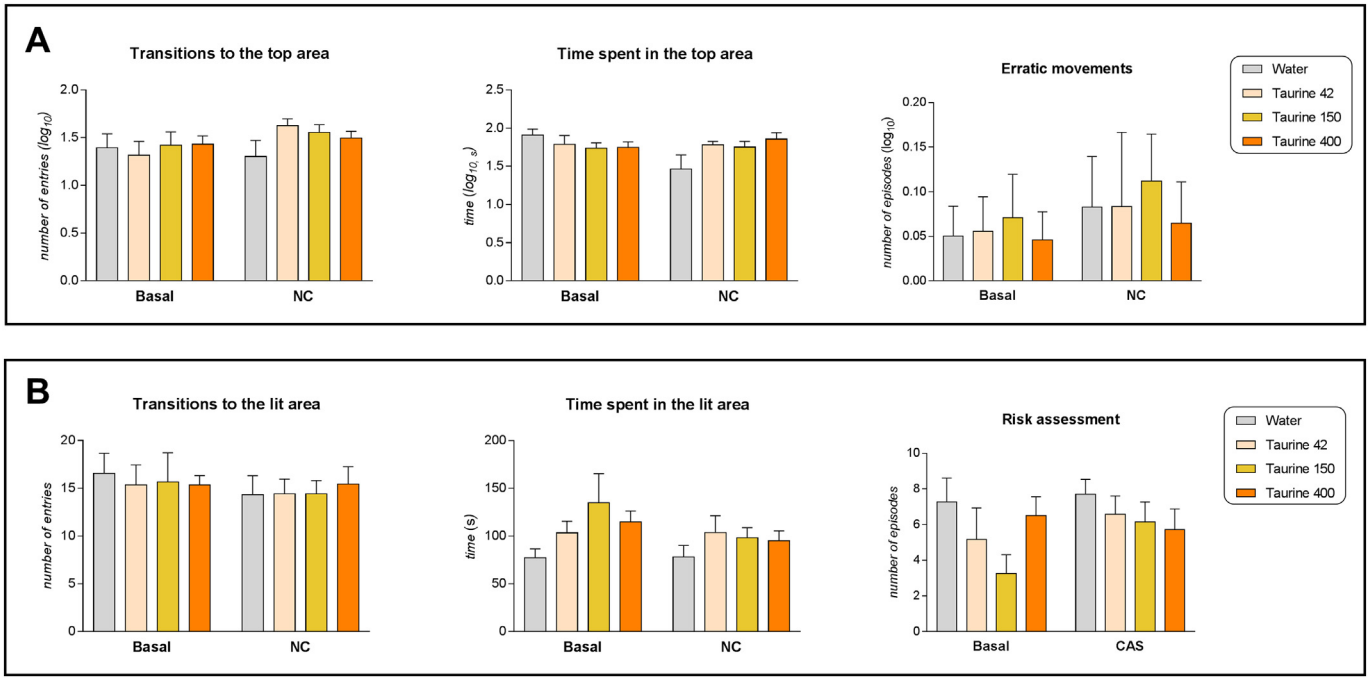

Fig. 2. Behavioral effects of taurine on net chasing-induced mechanical stress. (A) Novel tank diving test. (B) Light–dark test. Data were expressed as mean ± S.E.M and analyzed by two-way ANOVA, followed by Student–Newman–Keuls multiple comparison test. Statistical significance was set at $P \leq 0.05$. Asterisks above bars express significant differences compared to the control group, while asterisks above brackets indicate statistical differences compared to the NC group (n = 10–14 animals per group; NC: net chasing).

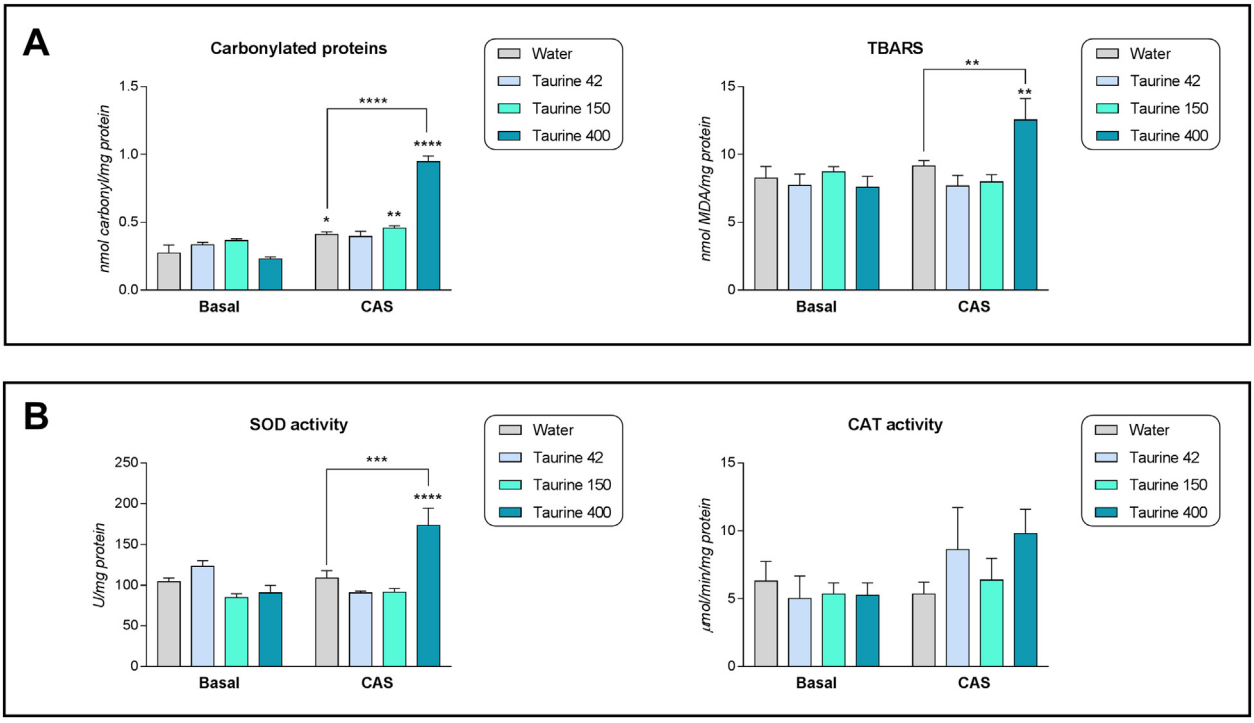

Fig. 3. Effects of taurine on CAS-induced chemical stress in biochemical analyses (A) Oxidative stress-related parameters. (B) Antioxidant defenses. Data were expressed as mean ± S.E.M and analyzed by two-way ANOVA, followed by the Student–Newman–Keuls multiple comparison test. Statistical significance was set at $P \leq 0.05$. Asterisks above bars express significant differences compared to the control group, while asterisks above brackets indicate statistical differences compared to the CAS group (n = 10–14 animals per group; CAS: conspecific alarm substance; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$).

for CAT [$F_{3,31} = 1.96$, $P = 0.1406$, gεs = 0.07], or SOD activities [$F_{3,33} = 2.10$, $P = 0.1184$, gεs = 0.08], a significant effect of the NC was observed for SOD [$F_{1,33} = 29.22$, $P < 0.0001$, gεs = 0.40] and CAT activities [$F_{1,33} = 19.92$, $P < 0.0001$, gεs = 0.32]. SOD activity was increased in taurine 150 and 400 groups, while CAT activity was potentiated with taurine 400 group subjected to chasing-induced stress.

3.3. Whole-body cortisol

Fig. 5 displays the effects of taurine on whole-body cortisol level.

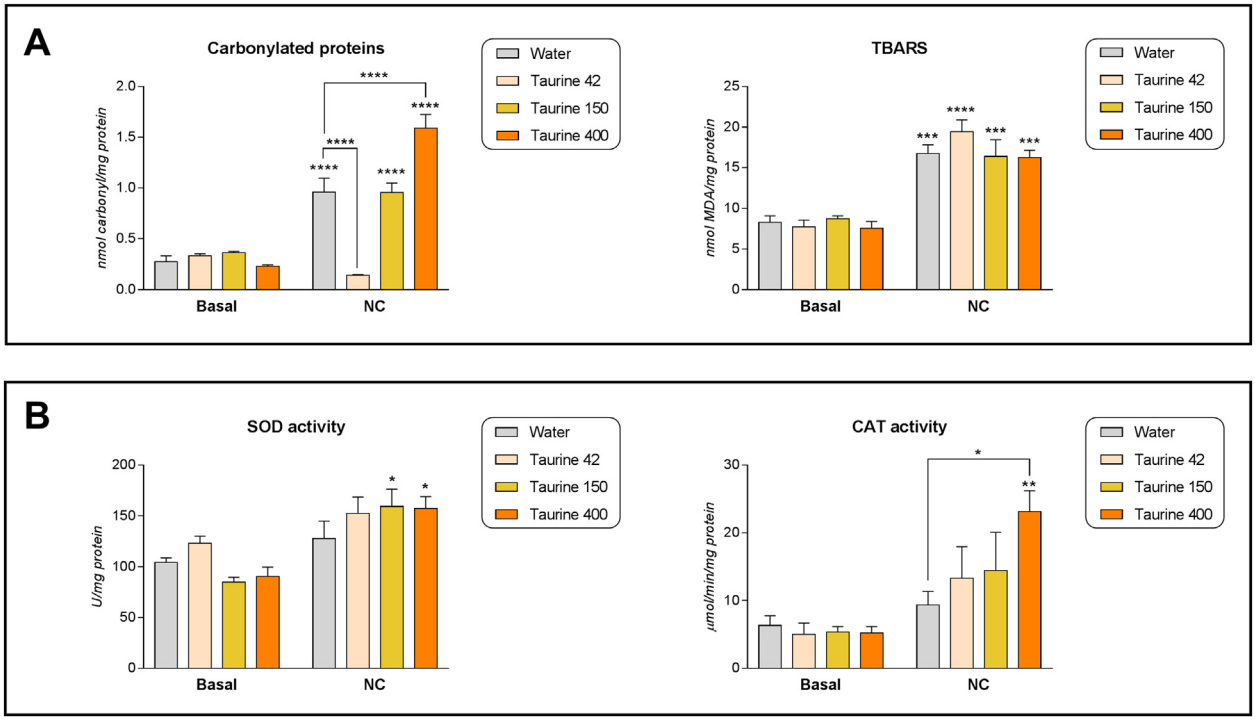

Fig. 4. Effects of taurine on net chasing-induced mechanical stress in biochemical analyses (A) Oxidative stress-related parameters. (B) Antioxidant defenses. Data were expressed as mean ± S.E.M and analyzed by two-way ANOVA, followed by Student–Newman–Keuls multiple comparison test. Statistical significance was set at $P \leq 0.05$. Asterisks above bars express significant differences compared to the control group, while asterisks above brackets indicate statistical differences compared to the NC group (n = 10–14 animals per group; NC: net chasing; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$).

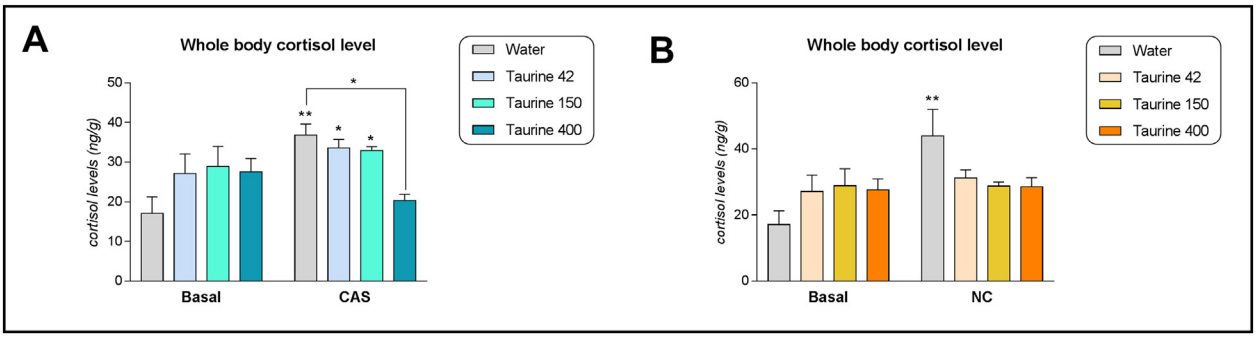

Fig. 5. Effects of acute taurine treatment on whole-body cortisol level (A) CAS-induced chemical stress. (B) Net chasing-induced mechanical stress. Data were expressed as mean ± S.E.M and analyzed by two-way ANOVA, followed by Student–Newman–Keuls multiple comparison test. Statistical significance was set at $P \leq 0.05$. Asterisks above bars express significant differences compared to the control group, while asterisks above brackets indicate statistical differences compared to the CAS/NC group (n = 10–14 animals per group; CAS: conspecific alarm substance; $^{*}P < 0.05$, $^{**}P < 0.01$).

The effects of taurine on CAS-induced chemical stress are showed in the Fig. 5A, where an interaction [$F_{3,33} = 5.12$, $P = 0.0051$, $g\varepsilon s = 0.26$], and CAS [$F_{1,33} = 5.33$, $P = 0.0273$, $g\varepsilon s = 0.09$] were detected. As a result, a preventive effect of taurine 400 exposed to CAS was observed.

The effects of taurine on chasing-induced mechanical stress showed in the Fig. 5B revealed a significant effect of the interaction ($F_{3,33} = 42.35$, $P = 0.0123$, $g\varepsilon s = 0.24$) and NC [$F_{1,33} = 62.51$, $P = 0.0176$, $g\varepsilon s = 0.12$]. No significant effects of the NC or treatment were observed.

4. Discussion

Herein, we show, at least to the best of our knowledge, for the first time a preventive effect of taurine on zebrafish stress responses. In fact, we observed that taurine abolishes some stress-related behaviors (*e.g.*, erratic movements and decrease in vertical exploration). Moreover, depending on the concentration tested, taurine prevents protein carbonylation and changes in whole-body cortisol levels (taurine 42 and taurine 400, respectively). We suggest that taurine may play a role against some behavioral, neurochemical, and physiological responses triggered by acute stressors in the zebrafish.

To understand stress-related conditions in experimental models, it is necessary to elucidate which stimuli affect defensive behaviors. Although the novel tank test evokes higher levels of cortisol, representing a more stressful procedure than the light–dark test alone (Kysil et al., 2017), both behavioral tasks are used to measure defensive behaviors following acute stress. Here, fish displayed fear- and anxiety-related behaviors after acute stress. More specifically, chemical stress seems to be more effective than mechanical stress to evoke fear-like responses in zebrafish. The net chasing protocol has been described as an effective stressor to fish, which induces a robust increase in whole-body cortisol levels (Abreu et al., 2014; Barcellos et al., 2011; Giacomini et al., 2016; Marcon et al., 2018; Mocelin et al., 2015), corroborating with the data shown here. Differently, CAS increases *c-fos*

expression in habenula (Ogawa et al., 2014) and exacerbates the frequency of erratic movements, suggesting fear (Parra et al., 2009; Speedie and Gerlai, 2008). Although these behaviors are adaptive avoidance responses of a stressful situation (Ferrari et al., 2010), the different contexts described here may serve as important factors in the dynamics of the stress responses that should be further investigated.

Although we did not observe all the anxiolytic-like effects of taurine alone described previously (Mezzomo et al., 2016), only the taurine 150 alone increased time spent to the lit area. Differences in the experimental protocol involving the time interval between the exposure period and the behavioral test could explain these discrepancies. Taurine plays multiple roles in the brain, including neuromodulation and inhibitory neurotransmission (Junyent et al., 2009; Menzie et al., 2014; Mezzomo et al., 2018; Rosemberg et al., 2010). This molecule acts as an agonist of $GABA_A$ and strychnine-sensitive glycine receptors and can directly interact with the NMDA receptor to suppress its activity (Chan et al., 2014; Poleszak et al., 2011; Zhang and Kim, 2007). Here, taurine prevented anxiety/fear-like behaviors depending on the context of the test. All taurine concentrations chosen abolished CAS-induced changes on erratic movements and geotaxis, which have been considered stress-related phenotypes. Anxiety is a trait typically associated with stressful situations, and the anxiolytic-like effects of taurine in zebrafish were described elsewhere (Mezzomo et al., 2016). Both acute and chronic stresses induce dephosphorylation and down-regulation of the K^+/Cl^- co-transporter, which affect the GABAergic control of CRF neurons, which activate physiological response to stress (Corteen et al., 2015; Maguire, 2014; Seifi et al., 2018). Thus, as the effects of taurine in vertebrates may involve $GABA_A$ activation (Mezzomo et al., 2018), this molecule emerges as a promising alternative strategy for treating stress-related disorders.

Stress disrupts redox homeostasis in the brain, leading to oxidative stress and impairing antioxidant enzyme activities (Dal Santo et al., 2014; Salim, 2017). The involvement of oxidative stress mechanisms has also been suggested in some psychiatric diseases including depression and fear- and anxiety-related disorders (Bouayed et al., 2009; Ng et al., 2008; Salim, 2017; Valko et al., 2007). Acute exposure to stressors increases oxidative stress in zebrafish brain (Dal Santo et al., 2014; Fontana et al., 2019; Maximino et al., 2011; Muller et al., 2018; Muller et al., 2017). The stressors of different natures assessed here stimulated oxidative parameters in all groups. Because taurine has antioxidant properties, this molecule may prevent oxidative stress in the brain (Lerdweeraphon et al., 2013; Rosemberg et al., 2010; Shimada et al., 2015). Here, the lowest concentration of taurine showed protective effects from protein carbonylation, while all other treatments did not prevent oxidative stress-related changes. Importantly, taurine alone did not influence the biochemical parameters measured. CAS- and net chasing-induced stress did not alter the enzymatic antioxidant defenses measured. Nonetheless, pretreatment with the highest taurine concentration stimulated SOD and CAT activities in fish subjected to CAS- and net chasing-induced stress, respectively. Although the lowest taurine concentration showed protective effects against oxidative stress-related changes, as well as stress-related behaviors following CAS exposure, our data do not reflect an associative concentration-dependent effect. Behavioral phenotypes represent complex responses resulting from a multifaceted interaction of various neurotransmitter systems and intricate cell signaling pathways under distinct conditions. Thus, other neurochemical parameters could play a key role in the responses measured here. In general, our results were similar to previous data describing a protective effect of taurine on PTZ-induced oxidative stress in zebrafish (Fontana et al., 2019). Possibly, the modulatory role of taurine on oxidation processes occurs by stimulating enzymatic antioxidant defenses. Vasodilator molecules like taurine increase CAT activity (Furian et al., 2009) and display an important function in controlling oxidative stress-related parameters (Das et al., 2012; Gurer et al., 2001; Parildar-Karpuzoglu et al., 2008). Although more studies are needed to clarify the neurochemical mechanisms underlying the effects of taurine, our data could reflect a compensatory mechanism that activates antioxidant defenses following a stressful situation.

Similar to humans, cortisol is the main stress hormone in zebrafish following the activation of the HPI axis (Alderman and Vijayan, 2012; Alsop and Vijayan, 2009; Baiamonte et al., 2015). As previously mentioned, stress increases whole-body cortisol content in zebrafish (Fonseka et al., 2016; Giacomini et al., 2016; Oliveira et al., 2013; Tudorache et al., 2013). As expected, both CAS and net chasing protocols increased whole-body cortisol levels in zebrafish. Importantly, pretreatment with the highest taurine concentration dampens the cortisol response to stress. Benzodiazepines modulate the $GABA_A$ receptor with anxiolytic, hypnotic, and anticonvulsant properties (Gebauer et al., 2011; Low et al., 2000; McKernan et al., 2000). Taurine acts on the $GABA_A$ receptor, and its potential anxiolytic-like effects are relatively well known in vertebrate models, including zebrafish (Fontana et al., 2019; Mezzomo et al., 2016; Mussulini et al., 2013). Although the exact mechanisms of the biological response of stress are unclear, the use of taurine may serve as an alternative therapeutic tool without benzodiazepine-induced side effects (*e.g.*, sedation).

Usually, psychiatric research is focused on mechanistic explanations underlying fear and anxiety (anxiolytic *vs.* anxiogenic effects and neurochemical parameters involved). These symptoms naturally support the function to prepare the organism (*i.e.*, physiologically, cognitively, and behaviorally) for detecting and dealing with threats to survival. If some situations may be adaptive to stress, an important question about the consequences of treatment arises. To what extent is the treatment beneficial to dampen the stress response? We suggest the importance of developing new strategies to treat anxiety-, trauma-, and stressor-related disorders.

5. Conclusion

In summary, our results show a protective role of taurine against stress-induced behavioral and biochemical changes in zebrafish. Taurine prevents anxiety/fear-like behaviors, protein carbonylation, and cortisol stimulation. Because taurine has beneficial effects in the brain, further studies are necessary to clarify the mechanisms underlying its neuroprotective role in vertebrates.

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Conflict of interest

The authors declare that no conflict of interest exists.

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6 DISCUSSÃO

Com estes estudos, mostramos que a taurina exerce efeitos modulatórios frente às situações de estresse e ansiedade em peixe-zebra. As concentrações testadas de taurina foram capazes de prevenir os comportamentos do tipo ansiedade e medo nos diferentes contextos. Contudo, a taurina desempenhou certa dualidade frente às situações de estresse. Enquanto a sua menor concentração preveniu a carbonilação de proteínas, a maior concentração estimulou excessivamente tanto parâmetros oxidativos quanto antioxidantes, além de inibir o aumento dos níveis de cortisol. Esses dados indicam que dependendo da concentração, a taurina pode exercer atividade ansiolítica, antioxidante e antiestresse nessa espécie.

Apesar dos efeitos da taurina sempre terem sido objeto de interesse por nosso grupo de pesquisa, os questionamentos sobre o papel desse aminoácido no SNC instigaram nossos estudos envolvendo sua influência em modelos de doenças neuropsiquiátricas em peixe-zebra. A taurina é um dos aminoácidos mais abundantes no cérebro, com capacidade neuromodulatória (WU et al., 2008; SCHAFFER et al., 2010). E, os seus diferentes mecanismos de ação e relevância fisiológica começaram a ser investigados de forma lenta e fragmentada, apenas décadas mais tarde da sua descoberta.

As principais ações fisiológicas da taurina em mamíferos, as quais foram compiladas em nossa revisão sistemática, incluem: a neuromodulação, a osmorregulação, a estabilização da membrana e a ação antioxidante (FOOS e WU, 2002; SCHAFFER et al., 2010; LERDWEERAPHON et al., 2013; MENZIE et al., 2014). Dentre os efeitos neurobiológicos já descritos, os efeitos antioxidante e neuroprotetor foram previamente sugeridos em estudos relacionados à exposição aguda do etanol em peixe-zebra. As análises iniciais dos efeitos apontaram que o pré-tratamento com taurina diminui a atividade da acetilcolinesterase e a peroxidação lipídica no encéfalo de peixes expostos ao etanol (ROSEMBERG et al., 2010). Além disso, ela é capaz de antagonizar os efeitos do álcool, uma vez que previne o comprometimento motor em concentrações elevadas de etanol (ROSEMBERG et al., 2012). Esses achados iniciais suportaram a teoria da manutenção redox, da modulação enzimática e da neuroproteção da taurina em peixe-zebra.

Algumas hipóteses foram propostas para justificar as funcionalidades da taurina no SNC, que passou a ser conhecida como um neurotransmissor inibitório (WU e PRENTICE, 2010; CHAN et al., 2014), devido à sua capacidade de neuromodução. Contudo, para a classificação de um neurotransmissor, cinco critérios básicos devem ser levados em

consideração. De fato, como sugerido em nossa revisão, muitos aspectos suportam a existência de um "sistema taurinérgico" no SNC, em especial pela modulação GABAérgica, glicinérgica e glutamatérgica (OKAMOTO et al., 1983; ALBRECHT e SCHOUSBOE, 2005; WU et al., 2005; WU et al., 2008; CHAN et al., 2014; MENZIE et al., 2014). No entanto, ainda assim não se pode classificar a taurina como um neurotransmissor clássico, principalmente pela ausência de informações acerca de receptores específicos de taurina e seu armazenamento em vesículas pré-sinápticas.

Curiosamente, a taurina é estruturalmente similar ao neurotransmissor GABA, e atua concomitantemente com ele ativando receptores $GABA_A$, permitindo o influxo de íons cloreto nos neurônios pós-sinápticos, aumentando a inibição neuronal (EL IDRISSI e TRENKNER, 2003). Mais especificamente, diz-se que a taurina atua como agonista parcial dos receptores $GABA_A$ nas membranas sinápticas (QUINN e HARRIS, 1995). Ensaios eletrofisiológicos de ligação competitiva mostraram que a taurina é um agonista fraco do complexo receptor $GABA_A$ que interage com os locais de ligação sensíveis a bicuculina, deslocáveis ao muscimol, modulando a ligação de benzodiazepínicos de forma alostérica (BUREAU e OLSEN, 1991; FROSINI et al., 2004).

A taurina também age indiretamente sobre a transmissão excitatória, regulando a homeostase do Ca^{2+} intracelular após a comunicação excitatória do glutamato, prevenindo dano neuronal associado com a excitotoxicidade glutamatérgica (EL IDRISSI, 2006). Ao contrário do sistema GABAérgico, a taurina não interage diretamente com nenhum dos receptores de glutamato, assim como no local de reconhecimento de glicina sensível à estricnina dos receptores NMDA (EL IDRISSI e TRENKNER, 1999). Portanto, a taurina parece alcançar o mesmo objetivo de modulação da excitabilidade neuronal através de pelo menos dois efeitos independentes, efeito direto na função GABAérgica e indireto na neurotransmissão glutamatérgica (EL IDRISSI e TRENKNER, 2003). Dessa forma, a taurina é estudada como alternativa farmacológica para o tratamento de disfunções do SNC, em especial as neurodegenerativas, as quais compartilham fisiopatologia em comum por excitotoxicidade do glutamato, desequilíbrio do cálcio, estresse oxidativo e morte celular (MENZIE et al., 2014).

Neste contexto, destacamos em nossa revisão, uma série de modelos de doenças neuropsiquiátricas que podem apresentar abordagens interessantes para avaliar mecanismos moleculares subjacentes aos efeitos da taurina no SNC. A excitotoxicidade causada pelo aumento do tônus glutamatérgico nas doenças de Alzheimer e Parkinson, parece ser

mediada pela excessiva ativação dos receptores NMDA, o que culmina em um aumento do influxo de Ca^{2+} neuronal (MOLINOFF, 2012). E, a prevenção da morte neuronal associada à excitotoxicidade, pode ocorrer pelo bloqueio dos receptores glutamatérgicos (LIPTON e ROSENBERG, 1994; MATTSON, 2003). A taurina pode prevenir a neurotoxicidade causada pelo peptídeo β-amiloide na doença de Alzheimer por meio da ativação dos receptores de $GABA_A$ (LOUZADA et al., 2004), enquanto na doença de Parkinson, a taurina pode modular o sistema nigrostriatal (BIANCHI et al., 1998; ZHANG e KIM, 2007). Além disso, sabe-se que a taurina estimula a neurogênese durante o envelhecimento cerebral em modelos animais (GEBARA et al., 2015), e que a sua suplementação previne o declínio cognitivo (EL IDRISSI, 2008). Assim, a modulação da taurina via receptores de glutamato e $GABA_A$ parece ser uma abordagem interessante no tratamento dessas doenças.

A esquizofrenia é um transtorno mental grave caracterizado por sintomas positivos (alucinações, delírios) e negativos (retirada social, anedonia). Os pacientes geralmente apresentam estado mental confuso, interrupção da vida social, de expressão emocional, e falta de motivação (HEINRICHS, 2003; JENKINS, 2013; NASYROVA et al., 2015). A taurina parece estar envolvida na fisiopatologia da esquizofrenia, uma vez que há mudanças no seu metabolismo e da glutationa reduzida (GSH), as quais são importantes na regulação da resposta inflamatória e atividade redox (SCHULLER-LEVIS e PARK, 2003; HADDAD e HARB, 2005). Ademias, há evidências que associam essa patologia com a disfunção de uma subpopulação de receptores NMDA (COYLE et al., 2002; COYLE e TSAI, 2004; COYLE, 2006), e como já foi descrito anteriormente, a taurina pode antagonizar os efeitos glutamatérgicos, exercendo efeito neuroprotetor.

A epilepsia**,** caracterizada por crises convulsivas recorrentes e esporádicas, causa depressão transitória da consciência. O tratamento consiste na administração de fármacos que agem inibindo as correntes de sódio, ou no aumento da inibição GABAérgica (CZAPINSKI et al., 2005). Uma vez que os esses fármacos não exercem um controle significativo de convulsões em 30% dos pacientes, a busca de novas moléculas terapêuticas é indispensável (TORRES-HERNANDEZ et al., 2015). Portanto, a taurina pode ser útil como terapia adjuvante, uma vez que modula a neurotransmissão e inibe a hiperpolarização neuronal (SARANSAARI e OJA, 2008).

Nos transtornos relacionados ao estresse, a liberação descontrolada de glicocorticoides, principalmente de cortisol, pode desencadear transtornos mentais como ansiedade e depressão (HOLSBOER, 2000; NEWPORT e NEMEROFF, 2000; WALKER

et al., 2013; MORENO-PERAL et al., 2014). Em modelo de hipertensão induzida por estresse em ratos, a taurina conseguiu regular o eixo HPA e o sistema renina-angiotensina-aldosterona, prevenindo a hipertensão causada por estresse (LV et al., 2015). Em nossos trabalhos, demonstramos que a taurina desempenha efeitos do tipo ansiolítico sem ser sedativa (MEZZOMO et al., 2016), e do tipo antiestresse por modular as respostas neuroquímicas como a liberação de cortisol em peixe-zebra (MEZZOMO et al., 2019). Esses dados evidenciam que taurina pode servir como estratégia terapêutica em futuros estudos relacionados à neurobiologia do estresse.

Com a necessidade do melhor entendimento da etiologia e fisiopatologia dessas doenças, também descrevemos as principais contribuições do peixe-zebra nas pesquisas translacionais acerca de novas alternativas terapêuticas. Na revisão, descrevemos inúmeras informações sobre os genes e estratégias genéticas relacionadas aos modelos de patologias descritas nessa espécie. Ademais, os neurotransmissores do peixe-zebra são evolutivamente conservados e as estruturas cerebrais com suas respectivas correspondências em mamíferos são relativamente bem conhecidas na espécie (BRETAUD et al., 2004; WAGER e RUSSELL, 2013).

No estudo das doenças neurodegenerativas, é conhecido que o peixe-zebra possui o sistema dopaminérgico caracterizado tanto em estágios embrionários quanto em adultos (PANULA et al., 2010). Além disso, os mecanismos genéticos subjacentes que medeiam a neurogênese do sistema dopaminérgico também são conservados entre mamíferos e essa espécie (FILIPPI et al., 2007; RYU et al., 2007). Todavia, esses modelos não mostram a perda neuronal de forma permanente, o que é um fator limitante para um estudo mais aprofundado das doenças neurodegenerativas relacionadas ao envelhecimento.

Na modelagem da epilepsia, o peixe-zebra é um organismo promissor para a pesquisa de novos tratamentos, pois os modelos mutantes também são sensíveis a vários fármacos clinicamente utilizados (BARABAN et al., 2013). Os episódios convulsivos também podem ser modelados usando o pentilenotetrazol (PTZ) e o ácido caínico (BARABAN et al., 2005; ALFARO et al., 2011; MUSSULINI et al., 2013). Apesar desses fármacos induzirem comportamentos similares à doença, não desencadeiam os mesmos mecanismos que induzem os episódios convulsivos, limitando em parte a validade desse protocolo experimental.

Em relação à esquizofrenia**,** a modelagem pode ser induzida pela administração de dizocilpina (MK-801), antagonista do receptor NMDA, conhecida por provocar sintomas comportamentais em roedores semelhante aos que ocorrem seres humanos afetados pela doença (CLINESCHMIDT et al., 1982; DEUTSCH et al., 1997). Similarmente, os peixes expostos ao psicotomimético MK-801 apresentam hiperlocomoção, a qual é atenuada por antipsicóticos (SEIBT et al., 2010; SEIBT et al., 2011; SEIBT et al., 2012; MAASWINKEL et al., 2013). Também foram encontrados efeitos do tipo ansiolítico (SEIBT et al., 2010), redução de formação da memória (ANDERSSON et al., 2015) e comportamento social alterado (ZIMMERMANN et al., 2016) após exposição ao MK-801 nessa espécie. Pode-se dizer que este modelo químico é adequado para futuras investigações farmacológicas em protocolos de triagem de novos compostos. Porém, existem poucos modelos animais disponíveis para estudar déficit comportamental e cognitivo até o momento.

Nos transtornos relacionados ao estresse, de forma similar aos seres humanos, o peixe-zebra secreta cortisol como o principal hormônio liberado após a ativação do eixo HPI (ALSOP e VIJAYAN, 2009; ALDERMAN e VIJAYAN, 2012; BAIAMONTE et al., 2015). Diversos estressores aumentam rapidamente a liberação do cortisol em peixes, atingindo níveis significativos após 15 minutos (BARCELLOS et al., 2007; RAMSAY, J.M. et al., 2009; BARCELLOS et al., 2016). Além disso, há possibilidade de investigação da expressão de genes relacionados ao estresse durante a ontogênese, o que torna o peixe-zebra atrativo para estudos comportamentais, neuroquímicos, fisiológicos e epigenéticos. Todavia, apesar da mensuração do cortisol ser consistente com a resposta ao estresse, a medida desse marcador circulante em larvas e adultos ainda é difícil pelo pequeno tamanho dificultando o preparo da amostragem.

Após as inúmeras informações sobre as fisiopatologias e estratégias relacionadas aos modelos descritos na revisão, iniciamos as investigações das ações da taurina em transtornos mentais relacionados ao estresse nessa espécie. Primeiramente investigamos a possível atividade ansiolítica da taurina, e após os positivos resultados obtidos, decidimos também averiguar se ela poderia ter atividade antiestresse nessa espécie. Antes de iniciar a discussão dos próximos dois artigos experimentais, é importante salientar que não são muitos os estudos que verificaram a ações da taurina em peixe-zebra. Por isso, uma breve descrição dos efeitos mais analisados nessa espécie até o momento foi exposta na Tabela 2.

Tabela 2 - Efeitos biológicos da taurina em peixe-zebra

Efeitos	Referências	Acesso ao DOI
Neuromodulação	(ROSEMBERG et al., 2012) (ROSEMBERG et al., 2010)	10.1016/j.neuropharm.2012.05.009 10.1016/j.neulet.2010.06.062
• Na ansiedade	(MEZZOMO et al., 2016) (FONTANA. et al., 2019)	10.1016/j.neulet.2015.12.037 10.1007/s00213-019-05410-0
• No estresse	(MEZZOMO et al., 2019)	10.1016/j.yhbeh.2019.02.006
• Na agressividade	(FONTANA et al., 2016)	10.1016/j.pbb.2015.11.011
• Na sociabilidade	(FONTANA et al., 2018)	0.1016/j.jpsychires.2018.08.008
• Na crise convulsiva	(FONTANA et al., 2019)	10.1007/s12035-018-1107-8
• Na memória	(BERTONCELLO et al., 2019) (FRANSCESCON et al., 2020)	10.1016/j.pnpbp.2019.03.006 10.1016/j.neuint.2020.104710
Antioxidante	(ROSEMBERG et al., 2010) (HAMMES et al., 2012) (CHEONG et al., 2015) (LEE et al., 2017) (FONTANA et al., 2019) (MEZZOMO et al., 2019)	10.1016/j.neuroscience.2010.09.030 10.1007/s10620-011-1931-4. 10.1007/978-3-319-15126-7_65 10.1007/978-94-024-1079-2_50 10.1007/s12035-018-1107-8 10.1016/j.yhbeh.2019.02.006
Anti-inflamatório	(CHEONG et al., 2015) (CHEONG et al., 2017) (KIM et al., 2017) (LEE et al., 2017)	10.1007/978-3-319-15126-7_66 10.1007/978-94-024-1079-2_74 10.1007/978-94-024-1079-2_51 10.1007/978-94-024-1079-2_50

O aparato claro-escuro é um teste já validado para avaliação dos comportamentos do tipo ansiedade em peixe-zebra (MAXIMINO et al., 2010). Nele, os peixes são colocados em uma área de pouco conforto (área clara) e naturalmente buscam segurança na área mais escura (escototaxia) (KYSIL et al., 2017). Nesse aparato, os animais tratados com taurina passaram mais tempo na área clara e aumentaram o número de cruzamentos. Curiosamente, apenas os animais tratados com a concentração intermediária (150 mg/L) diminuíram o número de episódios de avaliação de risco.

As diferentes respostas dependentes de concentração desencadeadas pela taurina já foram documentadas em peixe-zebra (Tabela 2). Por exemplo, o tratamento agudo com taurina demonstra ter efeito bifásico no comportamento agressivo induzido pelo etanol, onde a concentração de 150 mg/L desencadeia efeito do tipo antiagressividade (FONTANA et al., 2016). Com relação à redução de episódios de avaliação de risco, esse fenômeno foi

novamente observado em outro teste comportamental, relacionado ao medo, onde os animais tratados com a concentração de 150 mg/L mostraram menos cuidado ao explorar o compartimento próximo a um predador (FONTANA et al., 2018). Por fim, considerando que a taurina não alterou padrões locomotores nos animais, sugerimos que o tratamento agudo nas concentrações testadas não induz sedação, mas diminui o comportamento relacionado a ansiedade e medo conforme a concentração nessa espécie.

Apesar de não termos a explicação precisa sobre os mecanismos envolvidos no efeito bifásico da taurina sobre o comportamento dos peixes, acreditamos que a ela possa estar atuando pelos diferentes sistemas de neurotransmissão descritos inicialmente (WU et al., 2005; ZHANG e KIM, 2007; CHAN et al., 2014). Experiências com receptores GABA recombinante revelaram que a taurina possui capacidade de interagir com receptores por meio de diferentes combinações de subunidades (HADLEY e AMIN, 2007). Nas subunidades clonadas de GABAρ1, a taurina induz um efeito bimodal, ou seja, modula negativamente as correntes de GABA quando presente em altas concentrações, mas positivamente em baixas concentrações (OCHOA-DE LA PAZ et al., 2008). Esse efeito pode ocorrer devido à transição da conformação *cis* para a *trans* da molécula de taurina mediante alterações na sua concentração (REYES-HARO et al., 2014).

Posteriormente a isso, no terceiro artigo, procuramos avaliar se a taurina também modula as respostas comportamentais e neuroendócrinas de estresse em peixe-zebra. A fim de melhor compreender as diferentes condições relacionadas ao estresse, decidimos analisar dois estressores de naturezas diferentes, um estressor mecânico (por perseguição aguda com a rede), e outro químico (por exposição à substância de alarme de coespecífico; CAS) com os mesmos aparatos comportamentais empregados no trabalho anterior. Verificamos que a taurina (em todas concentrações) previne os comportamentos relacionados ao estresse, tais como movimentos erráticos e diminuição da exploração vertical, causados pela exposição à CAS. A menor concentração de taurina (42 mg/L) também preveniu a carbonilação de proteínas desencadeada por perseguição com rede, e a maior concentração de taurina (400 mg/L) inibiu a liberação de cortisol frente resposta de estresse à CAS.

Ambas as tarefas comportamentais são bem utilizadas para medir comportamentos defensivos após o estresse agudo, no entanto, o novo tanque é considerado mais estressante do que o teste claro-escuro, pois evoca níveis mais altos de cortisol (KYSIL et al., 2017). Apoiando essa informação, nossos dados mostraram que os comportamentos defensivos foram observados apenas no novo tanque, indicando que os diferentes contextos são fatores

importantes para a melhor compreensão das respostas ao estresse. Dentre os protocolos de estresse agudo, a perseguição com rede é bem citada na literatura pela capacidade de aumentar os níveis de cortisol em peixe-zebra (BARCELLOS et al., 2011; ABREU et al., 2014; MOCELIN et al., 2015; GIACOMINI et al., 2016; MARCON et al., 2018), e isso foi confirmado em nosso terceiro trabalho. Por outro lado, o protocolo de exposição à CAS aumenta a expressão de *c-fos* (marcador de atividade neuronal após estímulos nocivos) em habenula (OGAWA et al., 2014), e exacerba a frequência de movimentos erráticos, sugerindo comportamento de medo (SPEEDIE e GERLAI, 2008; PARRA et al., 2009). Corroborando com esses dados, notamos que a exposição à CAS parece ser mais eficaz do que o estresse mecânico em evocar respostas semelhantes ao medo/ansiedade nos peixes.

O efeito ansiolítico da taurina sozinha dependente de concentração, não foi observado nesse artigo como no trabalho anterior (MEZZOMO et al., 2016). Apenas os animais tratados com a concentração de 150 mg/L passaram mais tempo na área iluminada, indicando tal efeito. A divergência entre os dois trabalhos pode ser explicada pela maior complexidade desse protocolo experimental, uma vez que os animais passam por um intervalo de tempo maior (equivalente ao tempo de tratamento e indução ao estresse aplicado) antes de serem testados nos aparatos comportamentais. Notamos também que o efeito protetor da taurina frente ao estresse foi dependente do contexto do teste, ou seja, todas concentrações de taurina evitaram os comportamentos de medo/ansiedade apenas quando expostos à CAS e testados em novo tanque.

A ansiedade é uma característica tipicamente associada a situações estressantes, e considerando que a taurina desempenha efeito ansiolítico, os resultados obtidos estão de acordo com o esperado. O estresse induz desfosforilação e regulação negativa do co-transportador K^+/Cl^-, afetando o controle GABAérgico em neurônios que ativam a resposta fisiológica ao estresse através de CRH (MAGUIRE, 2014; CORTEEN et al., 2015; SEIFI et al., 2018). Ao mesmo tempo, sob condições estressantes, os níveis de taurina no cérebro aumentam significativamente (EL IDRISSI e TRENKNER, 1999). Esses dados sugerem que a taurina possa desempenhar o seu efeito de neuroproteção através da ação agonística em receptores de glicina e $GABA_A$ após situações de estresse.

O estresse também interrompe a homeostase redox no cérebro, desencadeando estresse oxidativo e déficit das atividades de enzimas antioxidantes (DAL SANTO et al., 2014; SALIM, 2017). Observamos que os dois estressores estimularam os parâmetros oxidativos avaliados, e o pré-tratamento com taurina preveniu um deles, sugerindo uma

possível ação antioxidante já relatada em trabalhos anteriores (ROSEMBERG et al., 2010; LERDWEERAPHON et al., 2013; SHIMADA et al., 2015). Mais especificamente, a carbonilação de proteínas foi prevenida com a menor concentração de taurina. Por outro lado, a maior concentração de taurina estimulou em excesso os parâmetros oxidativos, o que pareceu ser uma exacerbação de espécies reativas. Ademais, apesar de nenhum estressor sozinho ter alterado as defesas antioxidantes enzimáticas, a associação com a maior concentração de taurina também estimulou as atividades de superóxido dismutase (SOD) e catalase (CAT) em peixes submetidos a estresse químico e mecânico, respectivamente.

Moléculas vasodilatadoras como a taurina aumentam a atividade da CAT (FURIAN et al., 2009) enquanto controlam estresse oxidativo (GURER et al., 2001; DAS et al., 2012). Em processos inflamatórios, a taurina é convertida e liberada de neutrófilos ativados como taurina-cloramina, um oxidante mais fraco e mais estável. A taurina-cloramina inibe a superprodução de ânion superóxido, óxido nítrico, e aumenta a expressão de proteínas antioxidantes, como heme oxigenasse-1, peroxirredoxina, tioredoxina, glutationa peroxidase e CAT (KIM e CHA, 2014; CHEONG e LEE, 2017). Embora sejam necessários mais estudos para esclarecer os mecanismos neuroquímicos subjacentes aos efeitos da taurina, nossos dados podem refletir um mecanismo semelhante a este após uma situação estressante.

Por fim, ao avaliamos a resposta neuroendócrina ao estresse, nós concluímos que ambos protocolos foram capazes de aumentar os níveis de cortisol de corpo inteiro em peixe-zebra. Interessantemente, apenas a maior concentração de taurina foi capaz de inibir por completo essa resposta do cortisol ao estresse. Semelhante aos benzodiazepínicos, a taurina também parece modular o receptor $GABA_A$ com propriedades ansiolíticas e anticonvulsivantes nessa espécie (MUSSULINI et al., 2013; MEZZOMO et al., 2016; FONTANA. et al., 2019). No entanto, diferente dessa classe de fármacos, a taurina não apresenta sedação como efeito colateral, o que pode ser vantajoso como ferramenta terapêutica alternativa em transtornos mentais relacionados ao estresse.

É importante ressaltar que a taurina sozinha não influenciou nenhum parâmetro neuroquímico medido, e os últimos dados obtidos parecem não refletir apenas um efeito dependente de concentração como observado no estudo anterior. Isso significa que, frente ao estresse, o efeito desencadeado pela taurina pode depender da concentração, do contexto do teste e da natureza do estressor.

Diferente do primeiro estudo, o qual todas concentrações de taurina modularam os comportamentos do tipo ansiedade, nesse último estudo, vimos a taurina desempenhar um efeito dualístico nas concentrações extremas. Tal particularidade foi observada nas situações de estresse, uma vez que a taurina preveniu a carbonilação de proteínas em sua menor concentração, ao mesmo tempo que estimulou excessivamente os parâmetros oxidativos e antioxidantes, além de inibir o aumento dos níveis de cortisol em sua maior concentração. Tanto os fenótipos comportamentais, quanto neuroquímicos que foram aqui apresentados, representam respostas complexas resultantes de uma da possível interação com diferentes subunidades de receptores e vias intrínsecas de sinalização celular discutidas anteriormente.

A pesquisa no campo da psiquiatria normalmente está focada em explicações puramente mecanicistas envolvendo respostas de medo e ansiedade, as quais naturalmente têm função de detectar e preparar o organismo frente às situações de ameaça. Por isso, é importante refletir em quais situações patológicas seria benéfico inibir essa função fisiológica de resposta ao estresse. Aqui, nós demonstramos que a taurina é capaz de exercer diferentes ações de neuroproteção, demonstrando ter efeito do tipo ansiolítico e antiestresse em peixe-zebra. Assim, parece ser razoável sua indicação em novas pesquisas científicas mais aprofundadas no desenvolvimento farmacológico direcionado aos transtornos mentais, principalmente em transtornos de ansiedade, traumas e estresse crônico.

7 CONCLUSÃO

A partir desse estudo, ao buscar uma melhor compreensão das ações da taurina como tratamento dos transtornos mentais em humanos através do peixe-zebra, concluiu-se:

i. O peixe-zebra é um organismo modelo com grande potencial para a avaliação dos efeitos da taurina sobre parâmetros comportamentais e moleculares de diversos transtornos do SNC;
ii. A taurina modula as respostas comportamentais do tipo ansiedade em peixe-zebra, indicando ter efeito do tipo ansiolítico sem ser sedativo;
iii. A taurina modula as respostas neuroendócrinas do estresse em peixe-zebra, sugerindo ter efeito antiestresse.

8 PERSPECTIVAS

Após a verificação dos efeitos da taurina em nossos estudos com peixe-zebra, tais como a modulação do estresse (MEZZOMO et al., 2019), ansiedade (MEZZOMO et al., 2016), e agressão (FONTANA et al., 2016), a busca pela investigação das interações entre sistemas de neurotransmissores e vias intrínsecas de sinalização celular nessas condições, torna-se ainda mais fascinante.

Com base no fato de que a taurina pode interagir com outras vias de sistemas de neurotransmissores, parece ser razoável a investigação do envolvimento das vias serotoninérgica e dopaminérgica, as quais são comumente associadas ao comportamento do tipo agressivo (FILBY et al., 2010). Algumas evidências sugerem que uma hipofunção da serotonina, com a hiperfunção da dopamina, de maneira aditiva ao déficit serotoninérgico, pode predispor indivíduos à agressão. Essas interações disfuncionais entre os dois sistemas em córtex pré-frontal são relacionadas à agressão impulsiva e suas comorbidades (SEO et al., 2008; DAHLBOM et al., 2012).

Tanto o sistema de serotonina, quanto de dopamina são importantes no controle dos estados afetivos/defensivos relacionados ao estresse em peixe-zebra (SEO et al., 2008; MAXIMINO et al., 2013). Portanto, a verificação da interação da taurina com esses sistemas de neurotransmissores pode ajudar a elucidar as vias subjacentes que englobam a neurobiologia desses comportamentos relacionados ao estresse nessa espécie. Acreditamos que a melhor elucidação dessas interações nos processos fisiológicos, neuroendócrinos e comportamentais, fornecerão importantes descobertas para dados translacionais sobre a taurina que podem envolver o sistema serotoninérgico e dopaminérgico em seres humanos.

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iv. Fontana BD, Ziani PR, Canzian J, Mezzomo NJ, Müller TE, Dos Santos MM, Loro VL, Barbosa NV, Mello CF, Rosemberg DB. **Taurine Protects from Pentylenetetrazole-Induced Behavioral and Neurochemical Changes in Zebrafish.** Mol Neurobiol. 2019 Jan;56(1):583-594. doi: 10.1007/s12035-018-1107-8.

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vii. Fontana BD, Duarte T, Müller TE, Canzian J, Ziani PR, Mezzomo NJ, Parker MO, Rosemberg DB. **Concomitant taurine exposure counteracts ethanol-induced changes in locomotor and anxiety-like responses in zebrafish.** Psychopharmacology (Berl). 2019 Nov 30. doi: 10.1007/s00213-019-05410-0. [Epub ahead of print]

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ANEXO A – CARTA DE APROVAÇÃO Nº 026/2014

UNIVERSIDADE FEDERAL DE SANTA MARIA
PRÓ-REITORIA DE PÓS-GRADUAÇÃO E PESQUISA
COMISSÃO DE ÉTICA NO USO DE ANIMAIS-UFSM

CARTA DE APROVAÇÃO

A Comissão de Ética no Uso de Animais-UFSM, analisou o protocolo de pesquisa:

Título do Projeto: "Avaliação neuroquímica e comportamental dos efeitos promovidos pela taurina em peixe zebra expostos ao etanol: uma abordagem em modelos de exposição aguda e crônica".

Número do Parecer: 026/2014

Pesquisador Responsável: Prof. Drº Denis Broock Rosemberg

Este projeto foi **APROVADO** em seus aspectos éticos e metodológicos. Toda e qualquer alteração do Projeto, assim como os eventos adversos graves, deverão ser comunicados imediatamente a este Comitê.

OBS: Anualmente deve-se enviar à CEUA relatório parcial ou final deste projeto.

Os membros da CEUA-UFSM não participaram do processo de avaliação dos projetos onde constam como pesquisadores.

DATA DA REUNIÃO DE APROVAÇÃO: 08/05/2014.

Santa Maria, 08 de Maio de 2014.

Sonia Lucia Loro

Profª Drª Vania Lucia Loro
Vice - Coordenadora da Comissão de Ética no Uso de Animais- UFSM

Comissão de Ética no Uso de Animais - UFSM - Av. Roraima, 1000 – Prédio da Reitoria - 2º andar - Campus Universitário 97105-900 – Santa Maria – RS - - Tel: 0 xx 55 3220 9362

ANEXO B – CARTA DE APROVAÇÃO Nº 106/2014

UNIVERSIDADE FEDERAL DE SANTA MARIA
PRÓ-REITORIA DE PÓS-GRADUAÇÃO E PESQUISA
COMISSÃO DE ÉTICA NO USO DE ANIMAIS-UFSM

CARTA DE APROVAÇÃO

A Comissão de Ética no Uso de Animais-UFSM, analisou o protocolo de pesquisa:

Título do Projeto: "Mecanismos de ação da substância de alarme em diferentes linhagens de peixe-zebra (Danio rerio): Uma análise comportamental e bioquímica."

Número do Parecer: 106/2014

Pesquisador Responsável: Prof. Dr. Denis Broock Rosemberg

Este projeto foi **APROVADO** em seus aspectos éticos e metodológicos. Toda e qualquer alteração do Projeto, assim como os eventos adversos graves, deverão ser comunicados imediatamente a este Comitê.

OBS: Anualmente deve-se enviar à CEUA relatório parcial ou final deste projeto.

Os membros da CEUA-UFSM não participaram do processo de avaliação dos projetos onde constam como pesquisadores.

DATA DE APROVAÇÃO: 01/10/2014.

Santa Maria, 01 de outubro de 2014.

Vania Lucia Loro

Prof.ª Dr.ª Vania Lucia Loro
Vice-Coordenadora da Comissão de Ética no Uso de Animais- UFSM