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Juliano Ten Kathen Jung

EXERCÍCIO DE FORÇA PROTEGE DO FENÓTIPO DO TIPO ANSIOSO/DEPRESSIVO EM CAMUNDONGOS SUBMETIDOS A UM MODELO DE ESTRESSE

Santa Maria, RS, 2022

Juliano Ten Kathen Jung

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Dissertação apresentada ao curso de Mestrado do Programa de Pós-Graduação em Ciências Biológicas: Bioquímica Toxicológica, da Universidade Federal de Santa Maria (UFSM, RS), como requisito parcial para obtenção do título de **Mestre em Bioquímica Toxicológica.**

Orientador: Prof. Dr. Gilson Rogério Zeni

Coorientadora: Profª. Drª. Cristina Wayne Nogueira

Santa Maria, RS

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Aprovado em 18 de março de 2022:

Gilson Rogério Zeni, Dr. (UFSM)
(Presidente/ Orientador)

Cristina Wayne Nogueira, Drª. (UFSM)
(Coorientadora)

Ana Paula Pesarico, Drª. (UNESC)

Leonardo Magno Rambo, Dr. (UNIPAMPA)

Santa Maria/RS

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DEDICATÓRIA

A minha família, meu pai Remi, minha mãe Rosa, minha irmã Camila, por terem estado ao meu lado durante todo o percurso, me apoiando nos momentos ruins e vibrando nos bons;

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A educação e o ensino são as mais poderosas

armas que podes usar para mudar o mundo.

(Nelson Mandela)

RESUMO

EXERCÍCIO DE FORÇA PROTEGE DO FENÓTIPO DO TIPO ANSIOSO/DEPRESSIVO EM CAMUNDONGOS SUBMETIDOS A UM MODELO DE ESTRESSE

AUTOR: Juliano Ten Kathen Jung
ORIENTADOR: Gilson Rogério Zeni
COORIENTADOR: Cristina Wayne Nogueira

A díade ansiedade/depressão tem se mostrado um mal recorrente na população mundial nos últimos anos, sendo um fator incapacitante e agravado pelo fato de duas patologias centrais estarem associadas. O exercício físico de resistência tem sido estudado para além de seus efeitos a nível periférico, visando a melhora de pacientes depressivos, porém menos estudado se comparado a outras modalidades esportivas, como o exercício aeróbico. Deste modo, o objetivo desse trabalho foi avaliar o efeito protetor do exercício físico de resistência frente a díade ansiedade/depressão em camundongos machos expostos ao estresse e o envolvimento da neuroinflamação e neurogênese hipocampal. Este trabalho foi aprovado pelo Comitê de Ética no uso de animais sob número #1535120320. Camundongos Swiss machos (35 dias), divididos em dois grupos (sedentário e exercitado) iniciaram o protocolo de exercício de resistência , passando por uma semana de adaptação e nas quatro semanas seguintes havendo um incremento de cargas ao subir a escada a cada semana. Três dias após o fim do protocolo de exercício os animais foram redivididos e dois grupos foram expostos ao estresse, passando por testes comportamentais sete e oito dias após o estresse prolongado único emocional (E*sps*). Os resultados evidenciaram um efeito protetor do exercício de resistência frente as alterações causadas pela exposição ao estresse em testes preditivos de ansiedade e depressão. Este efeito do exercício está de alguma forma relacionado com sua capacidade de modulação de proteínas centrais envolvidas na neuroinflamação, que mostrou-se exacerbada em animais sedentários expostos ao estresse. Da mesma forma, o exercício mostrou modular a via proteína quinase B (Akt)/ alvo mecanístico da rapamicina (mTOR) no hipocampo, estrutura central associada com processos de neurogênese e alvo de estudos da fisiopatologia da díade ansiedade/depressão, além de evitar a diminuição do receptor de tropomiosina quinase B (TRκB) nesta estrutura. Tanto a exposição ao exercicio de força quanto a exposição ao estresse levaram a um aumento nos níveis de receptor de glicocorticoide (GR), o que demostra que os efeitos do exercício independem diretamente de GR. A exposição ao estresse levou ao aumentos dos níveis de corticosterona circulantes apenas em animais sedentários. Ambos, exercício de resistência e estresse não causaram danos locomotores nos animais. Em conjunto, os resultados aqui apresentados demonstram um papel protetor do exercício de força em camundongos machos submetidos ao estresse, pelo mesmo modular a neuroinflamação hipocampal, além de modular a via Akt/mTOR e a neurogênese.

Palavras-chave: Estresse. Depressão. Ansiedade. Exercício de Força

ABSTRACT

STRENGTH EXERCISE PROTECTS FROM ANXIOUS/DEPRESSIVE TYPE PHENOTYPE IN MICE SUBMITTED TO A STRESS MODEL

AUTHOR: Juliano Ten Kathen Jung
ADVISOR: Gilson Rogério Zeni
CO ADVIDOR: Cristina Wayne Nogueira

The anxiety/depression dyad has been a recurrent disease in the world population in recent years, being a disabling factor and aggravated by the fact that two central pathologies are associated. Resistance physical exercise has been studied in addition to its effects at the peripheral level, aiming at the improvement of depressive patients, but less studied compared to other sports modalities, such as aerobic exercise. Thus, the objective of this work was to evaluate the protective effect of resistance physical exercise against the anxiety/depression dyad in male mice exposed to stress and the involvement of neuroinflammation and hippocampal neurogenesis. This work was approved by the Ethics Committee on the use of animals under the number #1535120320. Male Swiss mice (35 days old), divided into two groups (sedentary and exercised) started the resistance exercise protocol, going through a week of adaptation and in the following four weeks, there was an increase in loads when climbing the stairs each week. Three days after the end of the exercise protocol the animals were divided and two groups were exposed to stress, undergoing behavioral tests seven and eight days after prolonged single emotional stress (Esps). The results showed a protective effect of resistance exercise against changes caused by exposure to stress in predictive tests of anxiety and depression. This effect of exercise is somehow related to its ability to modulate central proteins involved in neuroinflammation, which was shown to be exacerbated in sedentary animals exposed to stress. Likewise, exercise has been shown to modulate the protein kinase B (Akt)/mechanistic target of rapamycin (mTOR) pathway in the hippocampus, a central structure associated with neurogenesis processes and target of studies on the pathophysiology of the anxiety/depression-like dyad, in addition to preventing decrease of the tropomyosin kinase B (TRκB) receptor in this structure. Both exposure to strenght exercise and exposure to stress led to an increase in glucocorticoid receptor (GR) levels, demonstrating that the effects of exercise are directly independent of GR. Stress exposure led to increases in circulating corticosterone levels only in sedentary animals. Both strenght exercise and stress did not cause locomotor damage in the animals. Taken together, the results presented here demonstrate a protective role of resistance exercise in male mice subjected to stress, by modulating hippocampal neuroinflammation, in addition to modulating the Akt/mTOR pathway and neurogenesis.

Key-words: Stress. Depression. Anxiety. Strenght Exercise

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LISTA DE ABREVIATURAS E SIGLAS

ISMA-BR – International Stress Management Association no Brasil

CRH – Hormônio Liberador de Corticotrofina

ACTH – Hormônio Adrenocorticotrófico

CORT – Corticosterona

EIC – Estresse Imprevisível Crônico

EPU – Estresse Prolongado Único

OMS – Organização Mundial da Saúde

SARS-CoV-2 – Síndrome Respiratória Aguda Grave do coronavirus-2

5-HT –Serotonina

GC – Glicocorticoides

IL-6 – Interleucina-6

PGE-2 – Prostaglandina E2

PCR – Proteína C reativa

TNFα - Fator de necrose tumoral α

5-HT1A – Receptor de serotonina 1A

5-HT3 – Receptor de Serotonina

CREB – Proteína de ligação ao elemento de resposta ao AMPc

BDNF – Fator Neurotrófico derivado do cérebro

AMPc – 3',5'-Adenosina monofosfato cíclico

TRκB – Receptor de tropomiosina quinase B

IL-1β – Interleucina 1β

CONCEA – Conselho Nacional de Controle de Experimentação Animal

mTOR – Alvo mecanístico da rapamicina

SNC – Sistema Nervoso Central

SNS – Sistema Nervoso Simpático

SNP – Sistema Nervoso Parassimpático

NLRP3 – Proteína 3 que contém domínio de pirina da família NLR.

LPS – Lipopolissacarídeo

EDC – Escala de Depressão de Cornell

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1 INTRODUÇÃO

1.1 DEPRESSÃO

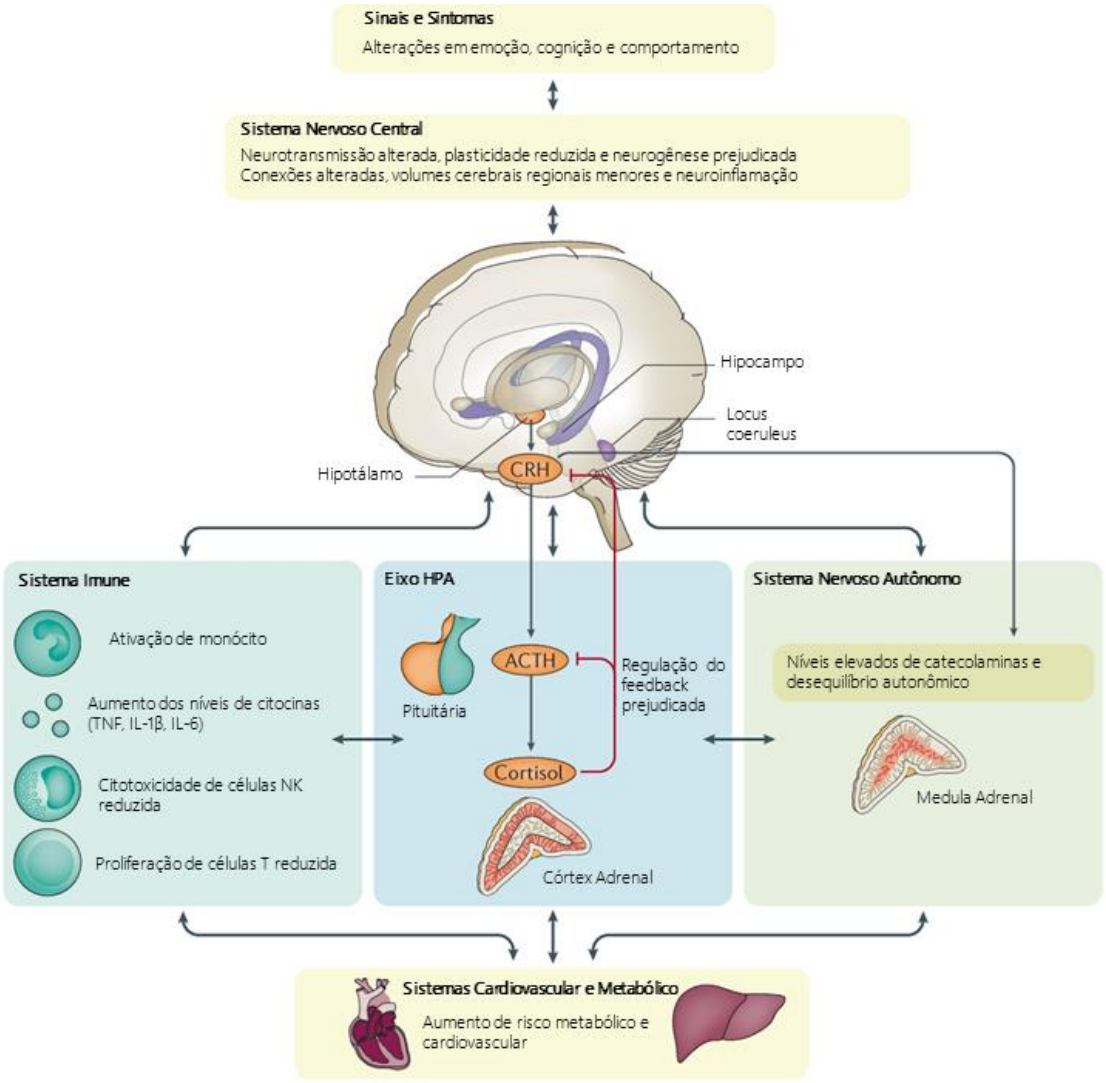
A depressão é um transtorno mental caracterizado por quadros de tristeza persistente, perda de interesse e vários dos seguintes sintomas: perda de energia, mudanças no apetite, aumento ou redução do sono, ansiedade, indecisão, culpa ou desesperança (SAÚDE, 2016). Segundo a Organização Mundial da Saúde (OMS) (UNITED NATIONS, 2020), houve um aumento nos sintomas de depressão e ansiedade em todo o mundo durante a pandemia causada pela síndrome respiratória aguda grave de coronavírus 2 (SARS-CoV-2). Na linha de frente, entre os mais afetados, figuram os profissionais da saúde. Profissionais da saúde chineses relataram altas taxas de depressão (50%), ansiedade (45%) e insônia (34%), enquanto no Canadá, 47% dos profissionais da saúde relataram a necessidade de suporte psicológico (UNITED NATIONS, 2020).

Estudos no campo da fisiopatologia da depressão (Fig. 1) tiveram avanços significativos nas últimas décadas, levando a várias hipóteses, porém a etiologia desta doença permanece desconhecida. A depressão é caracterizada por desregulações associadas a neurotransmissores, majoritariamente serotonina (5-hidroxitriptamina, 5-HT) e a noradrenalina (AGUIAR *et al.*, 2014). A hipótese do macrófago (SMITH, 1991), também conhecida como a hipótese das citocinas na depressão (MAES *et al.*, 2009; MILLER; MALETIC; RAISON, 2009), deduz que citocinas pró-inflamatórias são induzidas por macrófagos ativados ou situações de estresse crônico, alterando o *feedback* do eixo hipotálamo-hipófise-adrenal, pelo aumento da secreção de glicocorticoides (GC), desregulando seus receptores no hipocampo, o que pode resultar em morte neuronal e disfunção de neurotransmissores. As citocinas pró-inflamatórias podem desencadear quadros de falta de interesse, falta de prazer e outros comportamentos patológicos na depressão (SFORZINI *et al.*, 2019).

Interessantemente, algumas classes de antidepressivos incluindo inibidores seletivos da recaptação de serotonina e inibidores da recaptação de serotonina e noradrenalina podem ter ação também sobre a inflamação e o estresse oxidativo, mecanismos comumente alterados na depressão, podendo este ser um dos mecanismos que contribuem para que estas classes exerçam sua ação antidepressiva, como mostrado em testes pré-clinicos (ABDEL-SALAM; YOUSSEF

MORSY; SLEEM, 2011; HASHIOKA, 2011) e modelo clínico de condições neuropsiquiátricas(HAMER *et al.*, 2011). Porém, quando nos referimos ao sucesso nos tratamentos de depressão, temos que levar em conta o fato de que um terço dos pacientes não responde ao tratamento inicial, e quase metade dos pacientes não apresenta uma resposta ao tratamento considerada ótima, enquanto os efeitos colaterais oriundos da terapêutica são severos(ANTUNES *et al.*, 2015).

Figura 1: Sistemas biológicos envolvidos na patofisiologia da depressão

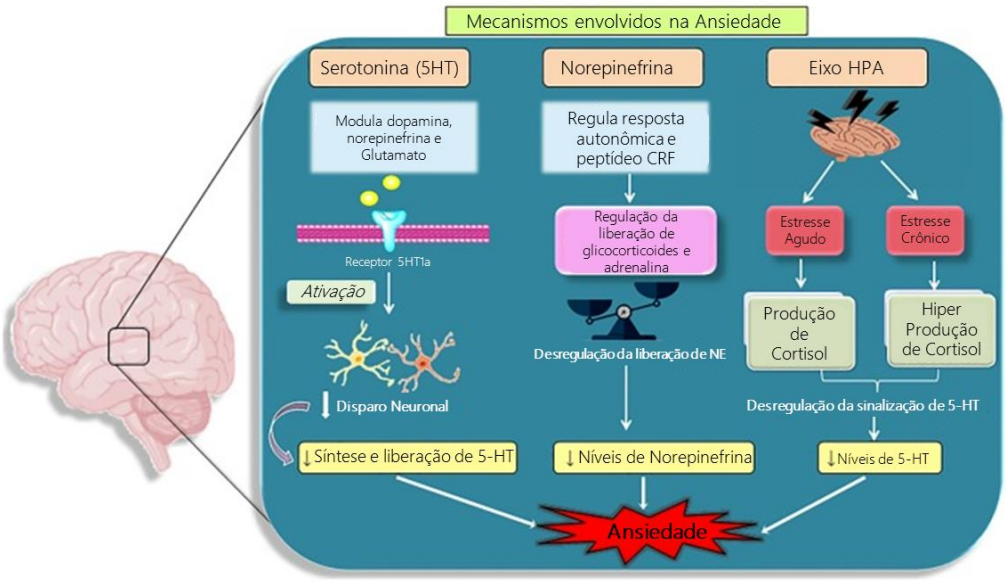


Fonte: Adaptado de (OTTE et al., 2016).

1.2 ANSIEDADE

Dados sobre a patofisiologia da ansiedade (Fig. 2) permanecem incompletos, além de biomarcadores confiáveis na clínica(BANDELOW *et al.*, 2017), porém já é sabido que respostas ao estresse e ansiedade em mamíferos são caracterizadas pela ativação de receptores β-adrenérgicos do sistema nervoso simpático (SNS) que ativa uma cascata de sinalização levando ao aumento da taxa respiratória, dilatação das pupilas, suor, liberação de adrenalina e noradrenalina, entre outras respostas (JOËLS; ANGELA SARABDJITSINGH; KARST, 2012). Somado a isto, o envolvimento do sistema serotoninérgico por meio de receptores 5-HT1A e 5-HT2A na ansiedade e estresse também tem sido elucidado, mostrando alterações nestes receptores em animais que apresentam comportamentos do tipo ansioso (XIANG *et al.*, 2019). A exposição ao estresse leva a uma ativação contínua do SNS, sem a ação de oposição do sistema nervoso parassimpático (SNP), resultando em um aumento dos níveis de catecolaminas e diminuição dos níveis de acetilcolina (CHARNEY *et al.*, 1987; KALK; NUTT; LINGFORD-HUGHES, 2011). O aumento de catecolaminas no sistema nervoso central (SNC), especialmente em áreas do sistema límbico levam a um aumento de citocinas pró-inflamatórias, sendo a liberação destas modulada por adrenalina e noradrenalina através de α e β-adreno receptores expressos em células imunes (CHARNEY; WOODS; HENINGER, 1989; EREN *et al.*, 2003). Won e colaboradores (2020) sugerem que mais estudos abordando o papel da neuroinflamação e biomarcadores associados a ela em quadros de ansiedade devem ser explorados para seu diagnóstico precoce e tratamento. Por ser um assunto comum no campo da fisiopatologia da depressão e ansiedade, abordaremos a neuroinflamação juntamente com a neurogênese no próximo tópico, por estas também estarem associadas.

Figura 2: Mecanismos envolvidos da patofisiologia da Ansiedade



Fonte: Adaptado de (KHATRI *et al.*, 2020).

1.3 NEUROINFLAMAÇÃO E NEUROGÊNESE

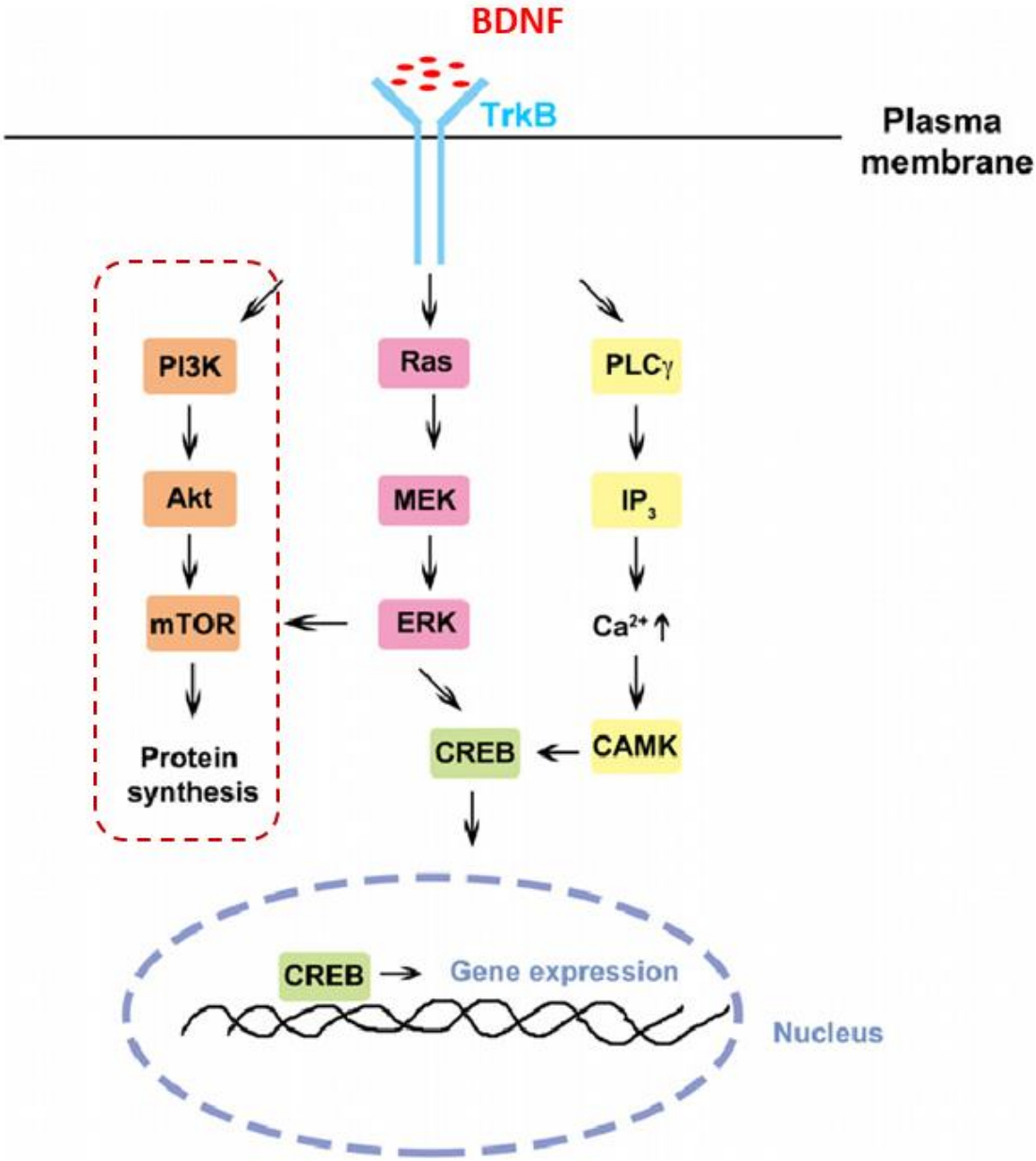
A micróglia, um tipo celular específico no sistema nervoso central, tem um papel importante na neuroinflamação, sendo a responsável pela eliminação de sinapses redundantes, processos de aprendizado e memória, desenvolvimento cerebral e envelhecimento(COLONNA; BUTOVSKY, 2017). Durante quadros de estresse, a micróglia torna-se ativa por ação do fenótipo pró inflamatório (M1) e do fenótipo anti-inflamatório (M2), o que pode ser conhecido por “ativação microglial” ou “polarização microglial”(FENG; FAN; CHUNG, 2020; ZHOU *et al.*, 2020). Uma vez ativado, o fenótipo microglial (M1) pode sintetizar e liberar citocinas como prostaglandina E2 (PGE2), proteína C reativa (PCR) e fator de necrose tumoral α (TNFα) na circulação sanguínea(ATTWELLS *et al.*, 2020).

A ativação microglial induzida por eventos estressores leva ao aumento da secreção de citocinas inflamatórias, como interleucina 1β (IL-1β) e 6 (IL-6), sendo estas as principais citocinas relacionadas a inibição da neurogênese em adultos. Como exemplo, IL-1β esta envolvida no dano à neurogênese induzida por interferon-γ(KANEKO *et al.*, 2006), especialmente sob condições de estresse(GOSHEN *et al.*, 2007; JA; DUMAN, 2008). O

inflamossoma NLRP3 é um receptor citoplasmático presente na micróglia no cérebro que pode ativar citocinas pró-inflamatórias como IL-1β (HIRSHMAN *et al.,* 2020). Estudos já demonstraram que disfunções comportamentais são observadas em modelos animais de depressão induzida por lipopolissacarídeo (LPS) acompanhada da elevação de citocinas pró-inflamatórias no hipocampo(LIANG *et al.,* 2017). Resultados semelhantes foram observados em camundongos com fenótipo do tipo depressivo induzido por estresse imprevisível crônico (EIC). A ativação do inflamossoma NLRP3 no hipocampo de camundongos está relacionada a comportamentos do tipo ansioso e depressivo, sendo estes melhorados com a redução da inflamação(XU *et al.,* 2016).

A neurogênese hipocampal em adultos tem se tornado alvo de pesquisas no campo da depressão induzida por estresse. Muitos pesquisadores hipotetizavam que neurônios maduros no cérebro não poderiam ser regenerados, mas evidências apontam que muitos neurônios novos continuam presentes nos cérebros de indivíduos maduros, especialmente no giro dentado no hipocampo (MAHAR *et al.,* 2014). Novos neurônios são formados do início ao fim da vida no hipocampo, porém em indivíduos depressivos a neurogênese hipocampal é prejudicada (SAHAY; HEN, 2007). O fator neurotrófico derivado de cérebro (BDNF) é a neurotrofina mais abundantemente distribuída no cérebro, sendo responsável pelo desenvolvimento neuronal, função e sobrevivência(BABU *et al.,* 2009). Neste sentido, observou-se uma diminuição dos níveis do receptor de tropomiosina quinase B (TRκB), alvo do BDNF, no cérebro de pacientes depressivos e vítimas de suicídio(CASTRÉN; KOJIMA, 2017; TRIPP *et al.,* 2012), indicando que a sinalização do BDNF por meio do receptor TRκB encontra-se prejudicada em pacientes depressivos. Além de outras vias ativadas por BDNF/TRκB, a cascata Akt/m-TOR é a principal via de sobrevivência mediada por TRκB que promove sobrevivência neuronal e protege frente a apoptose, que é um fator relevante para a depressão(JUNG *et al.,* 2008).

Figura 3: Via de Sinalização BDNF/mTOR



Fonte: Adaptado de (WANG et al., 2017).

1.4 ESTRESSE COMO INDUTOR DE DEPRESSÃO

O estresse mostra-se presente no dia-a-dia da população, podendo afetar emoções e processos cognitivos, estando intimamente associado ao desencadeamento de depressão, ansiedade e déficit cognitivo(XU *et al.*, 2015). Segundo a ISMA-BR (International Stress Management Association no Brasil), 70% do povo brasileiro é acometido por algum grau de estresse. A pesquisa também compara os níveis de estresse entre países, e o Brasil desponta atrás apenas do Japão, no quesito alto nível de estresse. Eventos estressantes geram memória e emoção aversivas, que servem como mecanismo para evitar exposições futuras ao evento

desencadeador(SOUZA; NOBLE; MCINTYRE, 2017a). O eixo hipotálamo-hipófise-adrenal, responsável pela produção de cortisol, é o eixo central relacionado ao estresse no corpo humano(WATKINS; JANE, 2006). A disfunção do eixo é majoritariamente causada pelo aumento da expressão do hormônio liberador de corticotrofina (CRH), hormônio adrenocorticotrófico (ACTH) e corticosterona (CORT)(JURUENA, 2014).

1.4.1 Modelos Animais de Estresse

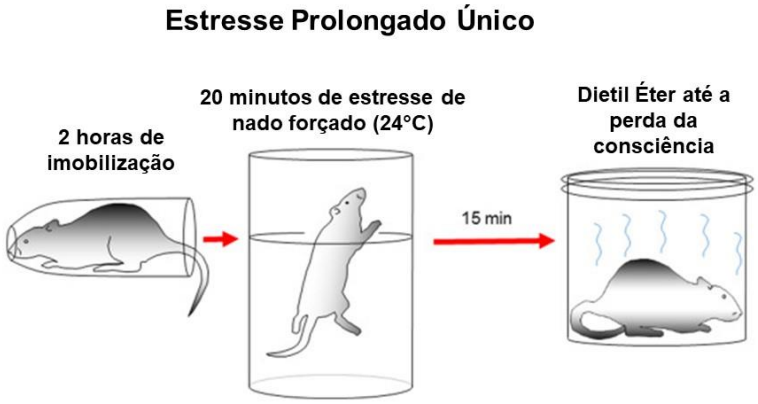
Modelos animais utilizando o estresse como desencadeador de quadros do tipo depressivos são muito bem consolidados na literatura(ABELAIRA; REÚUS; QUEVEDO, 2013; BIRMANN *et al.*, 2021; LIN; ZHOU; BOBROVSKAYA, 2021; ZHOU *et al.*, 2021). Um modelo muito utilizado é o estresse crônico moderado, no qual os animais são expostos, a períodos que variam entre três semanas a três meses, a diferentes estressores, como privação de água e de alimento, isolamento, exposição a baixas temperaturas(KATZ; ROTH; CARROLL, 1981). Apesar de ser um modelo robusto, os protocolos envolvendo este estresse demandam tempo do pesquisador, pelo protocolo ter um tempo de duração que variam entre 4 a 8 semanas(XIE *et al.*, 2019; ZHAO *et al.*, 2019).

Figurando entre os paradigmas pré-clínicos de aspectos do tipo depressivos induzidos por estresse está o estresse da derrota social, que apresenta um alto índice de relevância translacional, visto que o estresse social pode ser vivenciado praticamente diariamente por seres humanos(PRYCE; FUCHS, 2017). Uma das preocupações éticas acerca do paradigma de estresse da derrota social é o aparecimento de ferimentos no animal testado, como resultado dos ataques pelo animal agressor, o que pode refletir na integridade física do animal testado e no estudo em si(HENRIQUES-ALVES; QUEIROZ, 2016; TAKAHASHI *et al.*, 2017).

O estresse prolongado único (EPU) é composto de sucessivos estressores multimodais, sendo eles: imobilização, nado forçado e exposição ao dietil éter(LIBERZON; YOUNG, 1997) (Figura 3). Objetivando respostas ao estresse por três diferentes vias psicológica (contenção), fisiológica (nado forçado) e farmacológica (éter), este modelo, também consolidado, mostra-se preditivo de ansiedade e depressão, em testes comportamentais realizados sete dias após o protocolo de estresse(SOUZA; NOBLE; MCINTYRE, 2017b). Contudo, segundo a resolução normativa nº 37 do CONCEA, o uso de agentes de efeito lento, como o éter, é inaceitável em animais (CONCEA, 2018). Figurando como uma alternativa ao uso do éter, como agente

estressor, tem-se a utilização do odor do predador, por meio da maravalha utilizada nas caixas dos animais(PAPES; LOGAN; STOWERS, 2010), que tem sido empregada como um adicional estressor em modelos de estresse, visto que o éter ainda é utilizado em outros países em protocolos de estresse, como nos Estudos Unidos da América (PERRINE *et al.*, 2016). Um estudo em que ratos foram expostos em contato com odor do predador mostrou alterações no comportamento dos animais, deixando-os mais ansiosos e evidenciando neuroadaptação nos animais submetidos a este episódio estressante (LIANG; KING; ZHANG, 2014).

Figura 3: Protocolo de Estresse Prolongado Único.



Fonte: Adaptado de(TÖRÖK *et al.*, 2019).

1.5 EXERCÍCIO FÍSICO

Estudos abordando o exercício físico, uma ferramenta não farmacológica, em modelos animais têm demonstrado que o mesmo reverte o comportamento do tipo depressivo induzido por estresse imprevisível crônico e apresenta ação a nível central, como a modulação de proteínas relacionadas à plasticidade hippocampal(LIU *et al.*, 2017). O BDNF é crítico para estabilizar a plasticidade sináptica hipocampal e é um alvo gênico do tratamento antidepressivo junto com a cascata AMPc/CREB(MANJI *et al.*, 2003). O exercício físico aumenta a expressão de CREB/BDNF a nível hipocampal, o que reforça o papel do exercício regulando estas proteínas(LIU *et al.*, 2017). A maior parte dos protocolos de exercício utilizados como

ferramentas de estudo em modelos envolvendo camundongos são: exercício voluntário com presença de rodas nas gaiolas (HARE *et al.*, 2014; HUTTON *et al.*, 2015) e exercício em esteira(GRUHN *et al.*, 2021; SITENESKI *et al.*, 2020). A grande parte dos estudos que trazem o exercício físico como intervenção frente à depressão se baseiam, majoritariamente, em modelos de exercício aeróbico(LEGRAND; NEFF, 2016), apesar do exercício de força mostrar-se benéfico no manejo de condições de saúde severas como redução da obesidade e melhorando a sarcopenia (SCHLITTLER *et al.*, 2016).

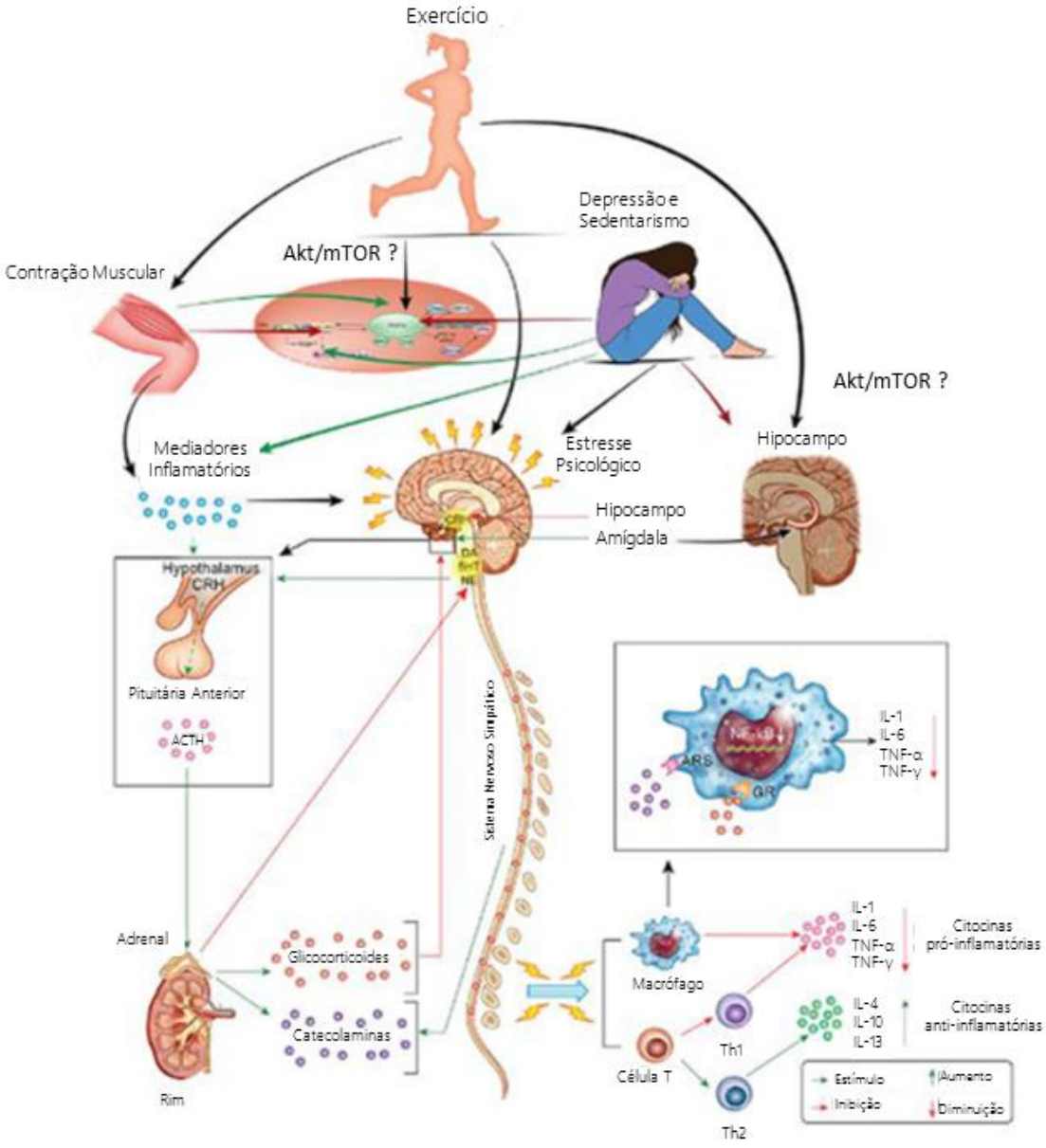
1.5.1 Exercício Físico de Força

O exercício de força tem se mostrado uma importante ferramenta, tanto preventiva quanto de tratamento para patologias associadas ao SNC, como depressão e doença de Parkinson por promover uma melhora no status neuroquímico, podendo este estar relacionado ao aumento da força muscular e performance física (TUON *et al.*, 2014).Liu e colaboradores (2021)demonstraram em um modelo de estresse crônico em ratos que existe uma associação entre perfil metabólico dos músculos sóleo e gastrocnemio com o fenótipo depressivo e que o exercício de força induz várias vias metabólicas no tecido esquelético e que estas estão diretamente envolvidas na melhora das respostas ao estresse. Interessantemente, em ratos saudáveis, tanto o exercício de força e aeróbico mostraram não terem significativas diferenças em parâmetros de ansiedade, além de não diferirem quanto a análises de indicadores de plasticidade sináptica hipocampal (SEGABINAZI *et al.*, 2020).

O exercício de carga progressiva é amplamente utilizado para estudar a intervenção do exercício de força na depressão. Chen e colaboradores (2017) utilizaram exercícios de força com banda elástica para melhorar os sintomas depressivos em pacientes com doença de Alzheimer. Sessenta e cinco idosos (65 anos) foram treinados por 15 meses (três vezes por semana, 40 minutos), e o escore da Escala de Depressão de Cornell (EDC) diminuiu após o exercício, com melhora significativa encontrada na disfunção de membros inferiores e distúrbios do sono ($P < 0,05$). Embora o exercício de força tenha provado ter efeito antidepressivo, é mais difícil implementar o exercício de força no plano de exercícios do que o exercício aeróbico. O exercício de força requer maior habilidade e equipamentos, o que é um obstáculo potencial, e estudos de acompanhamento de longo prazo e descrições detalhadas da intensidade e tipo de exercício ainda são necessários para o exercício de força. Portanto, frente

as alterações causadas pelo estresse e seu envolvimento na fisiopatologia da depressão, o exercício físico de força apresenta-se como uma ferramenta econômica (MURRI *et al.*, 2019).

Figura 4: Efeitos do Exercício Físico aeróbico na depressão e ansiedade.



Fonte:Adaptado de (PHILLIPS; FAHIMI, 2018)

2 OBJETIVOS

2.1 OBJETIVO GERAL

Avaliar o efeito protetor do exercício físico de força frente à díade ansiedade/depressão e alterações hipocampais em camundongos machos submetidos a um protocolo de estresse emocional.

2.2 OBJETIVOS ESPECÍFICOS

- Determinar se o exercício físico de força é efetivo em prevenir comportamentos preditivos de ansiedade e depressão em camundongos submetidos a um modelo de estresse.
- Esclarecer as vias centrais associadas aos comportamentos do tipo depressivo e ansioso em camundongos submetidos a um modelo de estresse, bem como o efeito do exercício físico de força, investigando proteínas relacionadas com a neuroinflamação e neurogênese na estrutura central hipocampo.
- Caracterizar a resposta ao estresse pelos níveis de corticosterona circulantes e expressão do receptor de glicocorticoides (GR) no hipocampo de camundongos.

3. DESENVOLVIMENTO

O desenvolvimento desta dissertação está apresentado na forma de um manuscrito em fase de preparação. Os itens introdução, materiais e métodos, resultados, discussão e referências encontram-se descritos no próprio manuscrito.

Resistance Training Modulates Hippocampal Neuroinflammation and Protects Anxiety-Depression-like Dyad Induced by an Emotional Single Prolonged Stress Model

Juliano Ten Kathen Jung[1], Luiza Souza Marques[1], Vanessa Angonesi Zborowski[1] Cristina Wayne Nogueira[1], Gilson Zeni*[1]

[1]Laboratório de Síntese, Reatividade e Avaliação Farmacológica e Toxicológica de Organocalcogênios, Centro de Ciências Naturais e Exatas, Departamento de Bioquímica e Biologia Molecular, Universidade Federal de Santa Maria, Santa Maria, CEP 97105-900, RS, Brazil

Correspondence should be sent to:

Gilson Rogério Zeni

Departamento de Bioquímica e Biologia Molecular, Centro de Ciências Naturais e Exatas, Universidade Federal de Santa Maria, 97105-900, Santa Maria, RS, Brazil.

Phone: 55-55-3220-8140

FAX: 55-55-3220-8978

Email: gzeni@ufsm.br

ABSTRACT

Depressive patients usually present symptoms of concomitant anxiety, and the anxiety/depression dyad is still poorly explored in animal models. Stress is a triggering factor for anxious and depressive behaviors, and in animal models it can be classified as acute and chronic. The aim of this study was evaluate the protective role of resistance exercise in anxiety-depression-like dyad induced by the exposure to a model of stress. Male Swiss mice were exercised for four weeks. After they were subjected to an E*sps* protocol, seven days later they were submited to anxiety and depression predictive behavioral tests. Our results showed that resistance exercise was effective in preventing behavioral changes caused by exposure to E*sps*, such as increased immobility in FST and TST, decreased grooming time and open arms time (OAT%) and open arms entries (OAE%), in addition to an increase in the anxiety index. However, exercise per se did not present an antidepressant or anxiolytic effect. Interestingly, hippocampal glucocorticoid receptor (GR) levels were increased by both the E*sps* and resistance exercise protocol, as well as no change in corticosterone levels. E*sps* was shown to decrease the hippocampal levels of tropomiosin kinase B (TRκB), and exercise protected from this alteration. Resistance exercise proved to be effective in decreasing neuroinflammation caused by exposure to E*sps*, by protecting from the increase in levels of NLRP3, IL-1β, and TNFα as well as increasing the Akt/mTOR pathway in Swiss mice hippocampus. Together, our results demonstrate that resistance exercise shows to prevent the development of the anxiety/depression dyad in male swiss mice exposed to a E*sps* protocol by increasing the Akt/mTOR pathway and hippocampal neuroinflammation.

Keywords: Depression. Anxiety. Stress. Resistance Exercise.

1. Introduction

Considering that the most commonly used therapy for depression is still the clinical prescription of antidepressive drugs to treat patients with MDD and only 20 to 40% of the patients respond to these drugs (PANDARAKALAM, 2018; PITSILLOU *et al.*, 2019), non-pharmacological methods should be more studied, considering the safety and non-toxic side-effects. Exercise is a well-known non-pharmacological and lifestyle liked option to prevent the development of many pathological states (GUEDES *et al.*, 2020). When compared to aerobic exercise modalities, resistance exercise has been less studied for its role in depression/anxiety treatment or prevention (GORDON *et al.*, 2017). Kang et al. (2020) have demonstrated that an 8-week resistance training attenuated chronic unpredictable mild stress (CUMS)-induced depression-like behaviors in male rats, suggesting that resistance exercise could be a promissory approach to even prevent or attenuate MDD and anxiety.

Approximately 350 million people worldwide experience major depressive disorder (MDD), a common neuropsychiatric condition with multiple factors involved, such as genetic and environmental, and more than 75% of people in low- and middle-income countries receive no treatment (EVANS-LACKO *et al.*, 2018; JO *et al.*, 2015). The vast majority of MDD cases show high comorbidity between depression and anxiety and stress-related disorders (ASRDs), being those disorders not entirely distinct conditions in humans or animals (KAUFMAN; CHARNEY, 2000; STEIN *et al.*, 2017). The coronavirus disease 2019 (COVID-19) elevated the day-by-day life stressors, including unsafety feelings, stay-at-home orders, canceled social events (MCKEE; STUCKLER, 2020). According to Salari et al. (2020) prevalence of stress, anxiety, and depression as a result of the pandemic in the general population is 29.6, 31.9, and 33.7% respectively.

A recent study indicates that the neurobiology of stress leads to an abnormal hypothalamic-pituitary-adrenal (HPA) axis activity (HOFMANN *et al.*, 2021) and neuroinflammation responses (PARK; LEE, 2021). Chronic and acute protocols of stress are used in rodents to induce depressive- and anxiety-like behaviors, aiming to clarify the alterations caused to stress in central structures (NAHVI *et al.*, 2021; WANG *et al.*, 2021; ZHU *et al.*, 2022) once that the pathophysiology of anxiety and depression need more information.

Acknowledging the potential benefits of resistance exercise, this study evaluated if resistance exercise protects against anxiety-depression dyad in mice subjected to an emotional

single prolonged stress (*Esps*) protocol. The contribution of hippocampal plasticity and neuroinflammation to resistance training effects was also investigated in this model.

2. Materials and Methods

2.1 Animals

Male Swiss mice (aged 35 days) housed in polycarbonate cages were used in this study. They had free access to commercial feed (GUABI, RS, BRAZIL) and tap water. Animals were maintained under controlled room temperature conditions (22 ± 2 °C) and a 12-h light/12-h dark cycle, with a light cycle starting at 7:00 a.m. Animals were obtained from the Central Animal Laboratory of the Federal University of Santa Maria (UFSM) – Brazil and handled following the rules of the Committee on Care and Use of Experimental Animals Resources of UFSM (#1535120320).

2.2 Drugs

Cocktails of protease and phosphatase inhibitors and the bicinchoninic acid assay (BCA) were purchased from Sigma (Sigma-Aldrich Company, St. Louis, Missouri, USA). Prestained protein standard was obtained from Bio-Rad (Bio-Rad, São Paulo, Brazil). All other reagents were of analytical grade and obtained from standard commercial suppliers.

2.3 Experimental Protocol

Mice were kept in the animal facility room from postnatal (PND) day 21 to 35. At PND 35, the animals were divided into two experimental groups: Sedentary (non-exercised, n = 16) and Exercised (n = 16, mice were exercised from PND 42 to 67). From the end of the resistance exercise protocol (PND 67) to the beginning of E*sps* (PND 70), mice were not manipulated.

At PND 70, animals of both groups were divided into four groups (Fig. 1):

- Group I: Sedentary Control (non-exercised and non-stressed, n =8);
- Group II: Sedentary + E*sps* (non exercised and subjected to E*sps* at PND 70, n =8);

- Group III: Exercise Control (exercised and non-stressed, n =8);
- Group IV: Exercise + Es*ps* (exercised and subjected to E*sps* at PND 70, n =8).

After mice had been subjected to the E*sps* protocol, they rested until the behavioral tests (PND 77 and 78). The body weight was accompanied, every two days, from PND 35 until PND 79.

2.3.1 Resistance Exercise Protocol

Animals of groups III and IV were trained using a 1-meter ladder, following a protocol previously published (KIM *et al.*, 2015). At PND 35 to 42, mice were familiarized with the ladder by climbing spontaneously with no added load (exercise adaptation). The protocol was performed by mice three times a week, on Mondays, Wednesdays, and Fridays, for 4 weeks (PND 42 to 67). The mouse body weight was measured before exercise to adjust the weight attached to the animal tail.

For every day of training, the mice were motivated to climb the ladder 15 times with a rest of 2 min between each climbing. Every week the weight attached to the tail was increased, beginning with 15% of the body weight in the first week, 30% in the second week, 50% in the third week, and ending with 75% of body weight in the last week (Fig.1). Mice were stimulated by touching their tails when they stopped climbing.

2.3.1.1 Maximum Carrying Capacity test (MCC)

The maximum voluntary carrying capacity test was performed by mice based on the methodology previously adapted from rats to mice (PEREIRA *et al.*, 2019). The test was carried out using a metal block mass in a small plastic microtube tied to the mouse tail. Under specific loads, mice should climb the ladder from bottom to top with less than three times of stimulation (touching their tails). We used 75% body weight as the first load of the training schedule and added 5 g sequentially if the mice could complete the task after a 5 min rest until the mice could not complete the task with three stimulations and/or even dropped down the ladder; then, the final mass value could be called the maximum capacity load. The test was performed on Friday, about 6 h after the exercise protocol, to full recovery of the animal in the adaptation week (MCC1), 30% body weight week (MCC2), and 75% body weight week (MCC3).

*2.3.2 Emotional Single Prolonged Stress (*E*sps) Protocol*

At PND 70, mice were individually immobilized for 2 h in an acrylic cylinder, with holes along the object to facilitate breathing. After that, each mouse was put to swim, in a cylindrical tank containing clean water at 25ºC for 15 min. To preserve animal welfare, the room was heated during the protocol, and the animals were dried with towels. They were placed in cages with excess wood shavings and remained for 15 min (recovery time)(LIBERZON; YOUNG, 1997) . Then, the animals were subjected to the last step of the protocol, which is exposure to the predator odor for 3 min. The predator odor consisted of a cage with shavings, urine, and fecal pellets of male rats. The exposure was carried out in another room (KONDOH *et al.*, 2016; SCHREIBER *et al.*, 2019). Animals did not have free contact with the bottom of the cage, being separated from it with a grid to avoid any contamination from rats urine and fecal pellets.

Non-stressed animals did not experience any stressful events. After the stress protocol animals rest for 7 days, beying in touch with humans only to food and water replacement.

At PND 77 and 78, mice performed behavioral tests. At PND 79, mice were killed by cervical dislocation (Fig.1). Hippocampus and plasma were collected and kept at -80ºC until the use. Triceps surae was also collected to determinate its weight.

2.4 Behavioral tests

The behavioral tests (n= 8/group) were carried out in two days to minimize stress in the animals.

2.4.1 Spontaneous locomotor activity

To evaluate exploratory capacity and exclude locomotion impairment after E*sps*, mice were tested in the spontaneous locomotor test. This behavioral test was performed in a clear acrylic apparatus (50 cm × 48 cm x 50 cm) connected to a monitor with photocell beams and containing 16 infrared sensors for the automatic recording of animal position and the general locomotor activity (Insight, SP, Brazil). Mice were placed in the center of the box and allowed to explore freely for 5 min. It was recorded the number of crossings, rearings and total distance traveled.

2.4.2 Elevated Plus Maze (EPM)

EPM was used to evaluate anxiety-like behavior in mice, according to the method described by Pellow et al (1985). The animals were individually placed in the central area of the maze facing an enclosed arm and were observed for 5 min. The apparatus was cleaned with an ethanol solution (10% v/v) and dried with paper towels after each trial. During a 5-min test period, the number of entries either the open or enclosed arms, plus the time spent in the open arms were recorded. An entry was defined as placing all four paws within the boundaries of the arm. The following measures were obtained from the test: (a) the time spent in the open/closed arms; (b) the number of entries into the open/closed arms. The percentage of time spent in the open arms, OAT% [(time spent in the open arms/total time spent in the arms) × 100], and the percentage of open arm entries, OAE% [(number of open arm entries/number of total arm entries) × 100], were calculated. The data were expressed as an anxiety index, which is calculated according to (DA COSTA ESTRELA *et al.*, 2015) as follows: Anxiety Index = 1 − [([Open arm time / Test duration] +[Open arms entries / Total number of entries]) / 2].

2.4.3 Tail suspension test

The tail suspension test was performed in a quiet experimental environment in which the total immobility duration is considered the major parameter measured to assess the "behavioral despair" rodents (STERU *et al.*, 1985). Mice were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. For the next 6 min, the latency for the first immobility episode and the immobility time was recorded. Mice were only considered immobile when passively hung and completely motionless.

2.4.4 Forced swim test

Originally described by Porsolt (PORSOLT; LE PICHON; JALFRE, 1977), the forced swim test is the most sensitive behavior test to evaluate antidepressant properties of new compounds. In this test, mice were individually forced to swim in an open cylindrical container (diameter 10 cm and height 25 cm) containing 19 cm of water at 25 ± 1 °C. Latency for the first immobility episode and total immobility duration (escape-related mobility behavior) were monitored for 6 min. Each mouse was considered immobile after it ceased struggling and began floating passively on the water.

2.4.5 Splash Test

The splash test was adapted from (YALCIN; AKSU; BELZUNG, 2005). This test evaluates grooming behavior, defined as cleaning of the fur by licking or scratching, after vaporization of 10% sucrose solution onto the mice dorsal coat. The solution's viscosity prompts mice to initiate grooming behavior, with depressive symptoms characterized by an increased latency (idle time between spray and initiation of grooming) and decreased time spent grooming. Latency and time spent grooming were recorded for 5 min.

2.5 Biochemical determinations

2.5.1 Corticosterone Assay

Blood was collected by heart puncture using heparin and samples were centrifuged at 2000×g for 10 min. Briefly, 0.2 ml of mice plasma was extracted, as well as a standard corticosterone 10µg/ml with chloroform, centrifuged, extracted again with NaOH (0.1 M), and then exposed to fluorescence reactive without light for 2 h (ZENKER; BERNSTEIN, 1958). Fluorescence was determined was measured at 247 nm for excitation and 540 nm for emission. The fluorescence intensity was expressed as µg/ml.

2.6 Western Blot Assay

Hippocampus samples (30 µg protein/well) and a marker protein (Bio-Rad, SãoPaulo, Brazil) were separated on an SDS-polyacrylamide gel by electrophoresis. The proteins were transferred to a nitrocellulose membrane (0.45 µm, Bio-rad) using the Transfer-Blot® Turbo ™ transfer system (1.0 mA, 15 to 40min, Bio-Rad). After blocking with 3% bovine serum albumin (BSA) solution for 1 h, the blots were incubated overnight at 4 ◦C with primary antibodies (Table S1). The method was performed as previously described by Rodrigues et al. (2022).

2.7 Statistical analysis

The data were expressed as the mean ± standard deviation (S.D). Initially, data normality was verified using D'Agostino and Pearson omnibus test, excepting the proteins from the western blot, in which the Shapiro-Wilk test was used. Comparisons among experimental groups were performed by Two-way analysis of variance (ANOVA) [E*sps* and exercise] followed by Tukey's multiple comparison test, excepting the data on the MCC test and weight, that were analyzed by repeated-measures ANOVA.

3. Results

3.1 Resistance training reduces the weight gain in exercised mice and enhances the triceps surae weight

The two-way analysis of body weight data demonstrated a significant difference for resistance training × time interaction ($F_{5,150}$ = 16.89; p< 0.0001). Exercised mice gain less weight than sedentary ones from weeks 3 to 5 (Figure 2A)(Table S2). As shown in figure 2B, exercised mice increased their maximum carrying load capacity during the protocol ($F_{1.873,28.1}$= 38.43; p< 0.0001)(Table S2). The triceps surae weight/ total body weight ratio showed no interaction between factors (exercise × stress) (Table 2S).

3.2 Resistance training and Esps do not induce locomotor alterations in mice

Locomotor activity profile was similar among mice subjected to a resistance exercise and E*sps* protocol (Figures 2C, 2D, and 2E)(Table S3).

3.3 Resistance exercise prevents a depressive-like behavioral phenotype induced by Esps exposure in mice

Sedentary mice exposed to E*sps* showed a statistically significant decrease in latency to immobility (Fig. 3A, $F_{1,28}$= 20.02; p=0.0032)(Table S3) and an increase in immobility time (Fig. 3B, $F_{1,28}$= 11.36; p<0.0001)(Table S3) in the TST when compared with the sedentary control group. Pre-exposure to resistance exercise was effective against the decrease in latency to immobility (p=0.0149) and the increase in immobility time (p<0.0001) in E*sps* mice.

Control exercised mice showed a decrease in latency to immobility (p=0.0227) when compared to sedentary control and a decrease in immobility time (p<0.0001) when compared to sedentary E*sps* in the TST (Figures 3A and 3B) (Table S3).

Exposure to E*sps* decreased the latency to immobility (Fig. 3C, $F_{1,28}$=30.86; p<0.0001)(Table S3) in the FST in control (p=0.0003) and exercise E*sps* (p=0.0002) groups when compared with a sedentary control group.

E*sps* statistically increased the immobility time (Fig. 3D, $F_{1,28}$= 9.503; p<0.0001)(Table S3) when compared with a sedentary control group in the FST, and this effect was abolished by resistance training (p=0.0008).

Figure 3E shows the effects of resistance training and E*sps* in the Splash test. Sedentary mice exposed to E*sps* had a statistically significant increase in latency to grooming ($F_{1,28}$=5.160; p=0.0281)(Table S3) and a decrease in grooming time (Fig. 3F, $F_{1,28}$=14.54; p=0.0289)(Table S3) when compared with a sedentary control group. Resistance training protected against the increase in latency to grooming (p=0.0063) and the decrease in grooming time (p=0.0041) in E*sps* exposed mice.

Figures 3B, 3D, and 3F illustrate that this resistance exercise protocol did not alter immobility time in the TST and FST, and grooming time on control mice when compared to sedentary control (Table S3).

3.4 Resistance exercise protects against anxiogenic-like behavioral phenotype induced by E*sps in mice*

Analyses of OAT% (Fig. 4A, $F_{1,28}$= 12.7; p=0.0028)(Table S3) and OAE% (Fig. 4B, $F_{1,28}$= 15.14; p<0.0001)(Table S3) data revealed a significant decrease in sedentary E*sps* exposed mice when compared with sedentary control. Resistance exercise protected against OAT% and OAE% in E*sps* mice (p<0.0001) when compared to the sedentary E*sps* group.

Figure 4C shows that sedentary mice exposed to E*sps* increased the anxiety index ($F_{1,28}$=13.97; p=0.0029)(Table S3) when compared with sedentary control. Resistance training protected against the increase in the anxiety index in E*sps* (p<0.0001) when compared with sedentary E*sps* mice.

Figures 4A, 4B, and 4C show that resistance exercise protocol did not alter parameters of anxiety in control mice when compared to sedentary control (Table S3).

3.5 E*sps exposure did not alter circulating corticosterone levels but increases hippocampal GR levels*

Plasma corticosterone levels were similar in all experimental groups (Fig 5A). The GR levels in the hippocampus of sedentary and exercised E*sps* mice were increased (Fig 5B, $F_{1,16}$=

4.573; p=0.0483)(Table S4) when compared with sedentary control. Resistance exercise per se increased the levels of GR in the hippocampus of mice when compared with sedentary control.

3.6 Resistance exercise protects against hippocampal neuroinflammation and NLRP3 inflammasome activation in E*sps mice*

E*sps* increased the hippocampal levels of TNFα (Fig. 6A, $F_{1,16}$=4.779; p=0.0377)(Table S4), NLRP3 (Fig. 6B, $F_{1,16}$=10.26; p=0.0127)(Table S4), and IL-1β (Fig. 6C, $F_{1,16}$=9,334; p=0.0114)(Table S4) in sedentary mice when compared with sedentary control. Resistance exercise protected the increase of TNFα (p=0.0114), NLRP3 (p=0.0019), and IL-1β (p=0.0063) levels in the hippocampus of mice exposed to E*sps* when compared with sedentary E*sps* group. Resistance exercise protocol did not alter hippocampal levels of TNFα, NLRP3, and IL-1β in control mice (Fig. 6A, 6B, 6C) when compared to sedentary control.

3.7 Resistance exercise protects against the decrease in hippocampal TRκB signaling in E*sps mice*

Data showed that sedentary mice exposure to E*sps* led to a decrease in hippocampal TRκB levels (Fig. 7A, $F_{1,16}$=5.504; p=0.0471)(Table S4) when compared to a sedentary control group. Resistance exercise protected against the decrease in levels of TRκB in the hippocampus of mice exposed to E*sps* (p=0.0005) when compared with sedentary E*sps*. Resistance exercise did not alter hippocampal TRκB levels in control mice when compared to sedentary control (Fig. 7A). proBDNF/mature BDNF ratio levels were similar in the hippocampus of mice from all experimental groups (Fig. 7B)(Table 4S).

Figure 8A shows that the p-Akt/Akt ratio was decreased by E*sps* exposure in the hippocampus of sedentary mice ($F_{1,16}$=22.54; p<0.0001)(Table S4) when compared to the control sedentary group. Resistance exercise was effective against the decrease in the ratio p-Akt/Akt when compared to the sedentary E*sps* group (p=0.0362).

The ratio of p-mTOR/mTOR was reduced in the hippocampus of E*sps* ($F_{1,16}$=12.83; p=0.0427)(Table S4) mice when compared with a sedentary control group. Resistance exercise increased the hippocampal p-mTOR/mTOR ratio in E*sps* exposed mice (p<0.0001) when compared with the sedentary E*sps* group (p<0.0001) (Fig. 8B).

Resistance exercise did not modify hippocampal p-Akt/Akt and p-mTOR/mTOR ratios in control mice when compared to sedentary control (Fig. 8A and 8B).

4. Discussion

Resistance exercise showed to prevent from the development of anxiety/depression dyad, neuroinflammation, activation of the inflammasome, and preserving the TRκB levels and Akt/mTOR pathway in the hippocampus. As far as we know, this seems to be the first study using a protocol of resistance exercise in mice before the exposure to stress. Our findings also indicate depression-like and anxiety-like phenotype in sedentary mice subjected to the E*sps* protocol, which was accompanied by a hippocampal increase of inflammatory cytokine levels, activation of the NLRP3 inflammasome, decrease in TRκB levels, and downregulation of the Akt/mTOR pathway (Fig. 9). Even though some differences in the experimental protocol, these findings corroborate with those of Lee (2016) and Lin (2020) showing an increase in anxiety-like behaviors caused by exposure to a stress model, in addition to depression-like behaviors (LEE; CHOI; SUR, 2020).

Depression and anxiety are highly comorbid, occurring concomitantly or sequentially (GORMAN, 1996). In animal models, behavioral tests can be considered analogous to the symptoms of depression and anxiety in humans (YANKELEVITCH-YAHAV *et al.*, 2015). Various reports show that single prolonged stress (SPS) can either produce or increase anxiety-like behaviors (LIN *et al.*, 2020; SUN *et al.*, 2020; ZHU *et al.*, 2022) as well as predator scent exposure (SIEVERT; LASKA, 2016; SOTNIKOV *et al.*, 2011).

Despair-like behaviors were observed after seven days of exposure to E*sps* by an increase in immobility time in TST and FST, increase in latency to grooming, and reduced grooming time, which characterizes depressive-like phenotype in rodents as described in previous studies (CRYAN; MOMBEREAU; VASSOUT, 2005; YANKELEVITCH-YAHAV *et al.*, 2015). Anxiety-like behavior was also observed in sedentary E*sps* exposed mice by a decrease in OAT% and OAE% and an increase in the anxiety index. These results taken together show consistency with those about stress models, causing anxiety-like and depressive-like behaviors (JUNG *et al.*, 2014; WINGO *et al.*, 2017).

Exercise has beneficial properties for muscle mass strength (DIAS RODRIGUES *et al.*, 2019), enhances cognitive function (SUIJO *et al.*, 2013), and improves short-term memory (KIM

et al., 2021) but there is a lack of information about resistance exercise if compared to aerobic exercise and its role in depressive-like and anxiety-like behaviors in mice. Our data showed that resistance exercise performed by mice for four weeks protected for depression-like and anxiety-like phenotype, by decreasing immobility time in the TST and FST, protecting against the decrease in grooming time, and the increase in the anxiety index. Our results are in agreement with those reported by Luo (2020), in which 6 weeks of aerobic exercise was effective in depressive-like mice. Moreover, an epidemiological study showed that aerobic or resistance exercise has similar antidepressant effects. The study was performed with 2724 elderly people with diagnosed depression from Taiwan, China, and evaluated frequency, duration, and intensity of exercise (CHEN *et al.*, 2012).

Our results revealed that circulating corticosterone levels were not altered in stressed mice. Kosti et al (2006) showed in a Maudsley rat model of emotionality that a 30 min restraint stress in Maudsley rats did not differ in their peripheral corticosterone response to acute restraint stress, but an exacerbated ACTH secretion response was observed, which may suggest an imbalance in adrenal cortex sensitivity. In addition, Sasse et al (2009) demonstrated that a 6 week of voluntary weel running facilitates corticosterone response habituation in Sprague-Dawley rats subjected to a 11-days loud noise stress protocol.

Regarding the hippocampal protein content of GR, the increse of GR in the CA3 hippocampal region of rats was demonstrated after an exporure to a modified SPS protocol, in addition to decrease in the levels of dopamine (DA) (SKÓRZEWSKA *et al.*, 2020). Being the exercise-CORT paradox something to be better explored, a wheel-running exercise protocol showed to modulate the pathway CORT, GR, (DA), and Dopamine receptor 2 (DR2) achieving an antidepressant-like effect of exercise in medial pre-frontal cortex of male rats (Chen et al., 2016), meanwhile, the model of exercise used in this study is different and we hypothesize that it can lead to different biological responses. Our results shows that exercise did not induce antidepressant- and antianxiogenic-like effects in control mice, once that this experimental group wasn't estatistically different of sedentary control.

Neuroinflammation in a general way is commonly related to depression-like behaviors in animals. The increase in cytokines in the hippocampus is closely related to a decrease in neurogenesis in this structure (VALLIÈ *et al.*, 2002). NLRP3 inflammasome activation mediates depressive-like behavior in rodents exposed to a chronic unpredictable mild stress (CUMS)(PAN *et al.*, 2014). Our data demonstrate an increase in NLRP3, TNFα, and IL-1β levels

in the hippocampus of anxious/depressed mice exposed to stress, showing a microglial superactivation and the release of pro-inflammatory cytokines. Zhang (2015) reported that the NLRP3 inflammasome is involved in stress-induced depression and plays a critical role between stress and depression, confirming that by blocking the NLRP3 inflammasome signaling through a highly selective caspase-1 inhibitor (VX-765).

Exercise has been reported to suppress NLRP3 inflammasome action and modulate neuroinflammation (ZHANG; DING; WANG, 2021), but the mechanisms are still unknown. Considering that NLRP3 can also be activated by oxidative stress, exercise may act by activating the endogenous antioxidant system (ABDERRAZAK *et al.*, 2015; TUON *et al.*, 2012). Exercise has also been shown to induce the expression of miR-223, an important mediator of neuronal development, that can either regulate TLR4/MyD88/NF-κB pathway signaling and NLRP3 inflammasome activation in the hippocampus of CUMS-depressed mice (QU *et al.*, 2020). A recent study (ORTIZ-LÓPEZ *et al.*, 2017)demonstrated the protective effects of exercise and fluoxetine on the development of depression and its comorbid anxiety disorders induced by stress in rats.

Brain-derived necrose factor (BDNF) plays a critical role in neurogenesis, cell proliferation, and the early cell survival phase. BNDF can exert its beneficial role through activating tropomyosin receptor kinase B (TRκB), which activates proteins involved in cell survival and migration pathways (ORTIZ-LÓPEZ *et al.*, 2017). Intrinsic and extrinsic factors can modulate the hippocampal neurogenesis, such as the activation of the HPA axis (SNYDER *et al.*, 2011) and consequent enhance the circulating glucocorticoids in response to stress exposure (ANACKER *et al.*, 2013) . These alterations may affect learning, memory, and mood, which can lead to a depressive state. On the other hand, TRκB overexpression in the hippocampus and cortex showed to decrease anxiety-like behavior in the EPM in mice (KOPONEN *et al.*, 2004). Aerobic Exercise enhances TRκB levels in the hippocampus in mice (FAHIMI *et al.*, 2016; LIU *et al.*, 2008), which can explain the elevated levels of this protein in the exercised groups.

Being the BDNF-TRκB interaction preserved, it can activate by phosphorylation various cascades, one of them is the Akt/mTOR pathway. Once Akt is phosphorylated it activates mTOR phosphorylation which will control the expression of proteins correlated with neuronal proliferation or survival (LIU *et al.*, 2015). Our findings demonstrate that stressed mice showed changes in Akt/mTOR pathway by the decrease in the phosphorylation ratio of these proteins. Stress shows to decrease the ratios of p-Akt/Akt and p-mTOR/m-TOR in the hippocampus and

cortex of mice (TANG *et al.*, 2015; XIA *et al.*, 2016), and the silencing of this pathway is directly linked with depression- anxiety-like behaviors in rodents. Some studies report the importance of TRκB/m-TOR signaling as a target to potential antidepressant molecules, once this pathway contributes to protein synthesis required for synaptic plasticity (SHEN *et al.*, 2018; ZHUANG *et al.*, 2016). Comparison between aerobic and resistance exercise has shown that 8 weeks of exercise improved depression behavior and reduced hippocampal neuronal apoptosis by acting differently, aerobic exercise activating PGC1α/ERRα/FNDC5 pathway, while resistance exercise show to up-regulate IGF-1/Akt/mTOR signaling pathway in a CUMS-induced depression model in rats (KANG; WANG; WANG, 2020).

In the present study, resistance exercise was a prophylactic tool to protect the onset of anxiety- depression-like dyad induced by Esps, by either preventing the increase of inflammatory cytokines in the hippocampus, activation of the NLRP3 inflammasome, and up-regulating the Akt/mTOR pathway in this structure. More studies are necessary to clarify the role of resistance exercise in a model of emotional stress-induced depressive/anxiety dyad and signaling pathways that can be involved with BDNF/TRκB signaling in different cerebral areas.

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6. CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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FIGURES

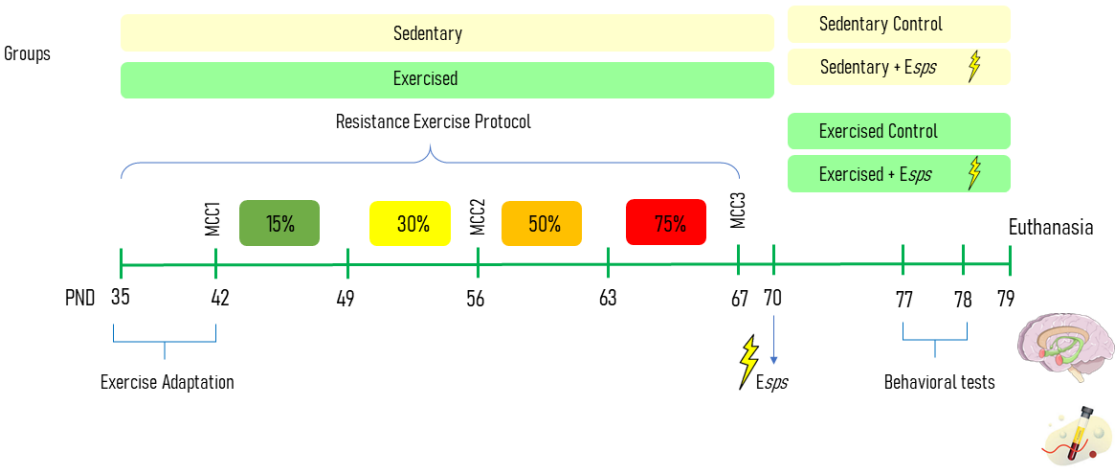


Fig. 1. Scheme of the experimental protocol. PND means postnatal day, E*sps* means emotional single prolonged stress.

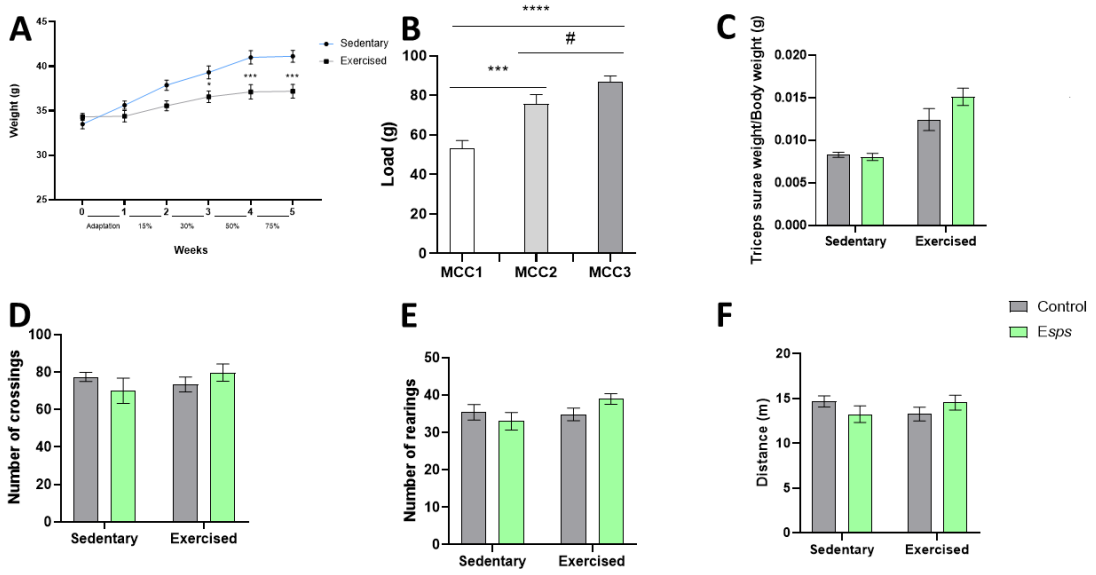


Fig. 2. Effects of resistance exercise on the total body weight gain (A), maximum carrying capacity test (B), triceps surae weight/total body weight (C), and the number of crossings (D), rearings (E), and distance traveled (F) by mice exposed to an E*sps* protocol. Results represent

the mean ± S.E.M. of 16 mice per group (A and B) and 8 mice per group (C-E). *P<0.05; ***P<0.001; ****P<0.0001 compared with a sedentary group (A) and compared with MCC1 (B), #P<0.05 when compared with MCC2; Two-way ANOVA with repeated measures followed by the Sidak's test (A); One-way ANOVA with repeated measures followed by the Tukey's test (B) and Two-way ANOVA followed by Tukey's post-hoc test (C-E). MCC, maximum carrying capacity; E*sps*, emotion single prolonged stress.

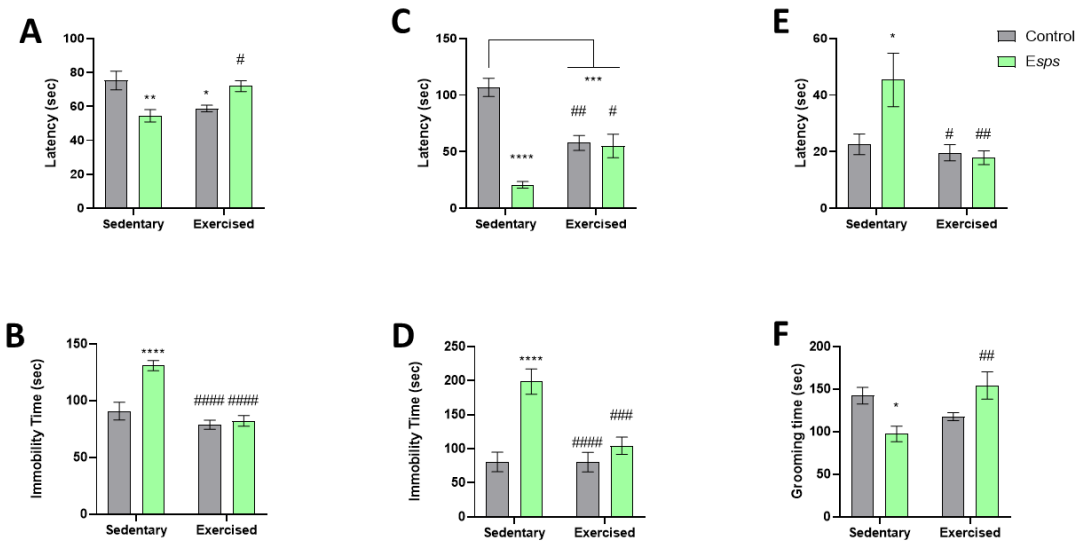


Fig. 3. Effects of resistance exercise on the TST (A and B), FST (C and D), and Splash test (E and F) on mice subjected to an E*sps* protocol. Results represent the mean ± S.E.M. of 8 mice per group. Data were analyzed by Two-way ANOVA followed by Tukey's post-hoc test when appropriate. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001 compared with sedentary control group; #P<0.05; ##P<0.01; ###P<0.001; ####P<0.0001 compared with sedentary E*sps* group. E*sps*, emotion single prolonged stress.

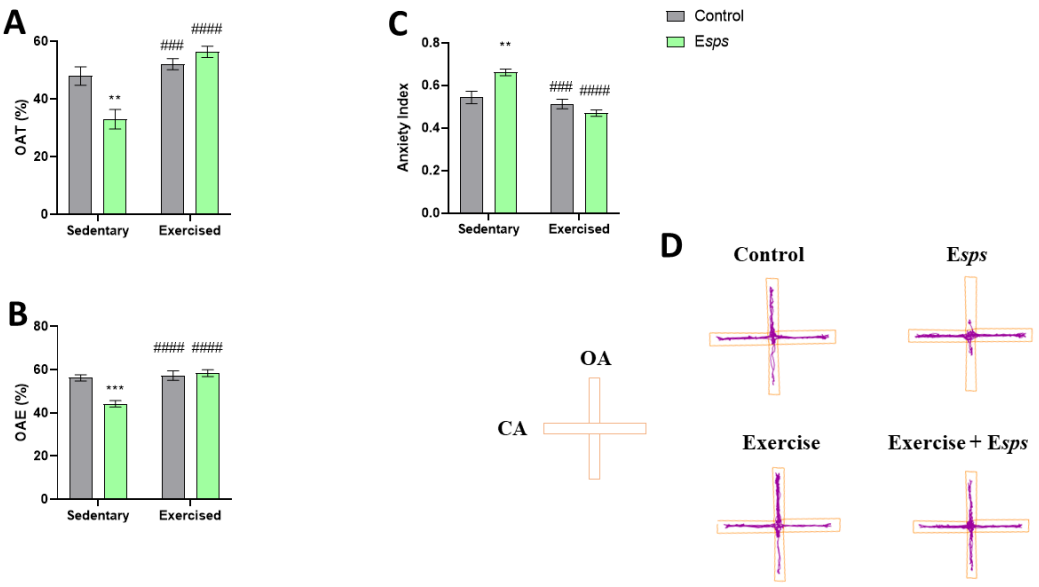


Fig. 4. Effects of resistance exercise on EPM parameters of anxiety, OAT% (A), OAE% (B), Anxiety Index (C), and representative images of animal performance in the EPM (D). Results represent the mean ± S.E.M. of 8 mice per group. Data were analyzed by Two-way ANOVA followed by Tukey's post-hoc test. **P<0.01; ***P<0.001; compared with the sedentary control group; ###P<0.001; ####P<0.0001 compared with the sedentary E*sps* group. E*sps*, emotion single prolonged stress; OAT%, open arms time; OAE%, open arm entries; CA, closed arms; OA, open arms.

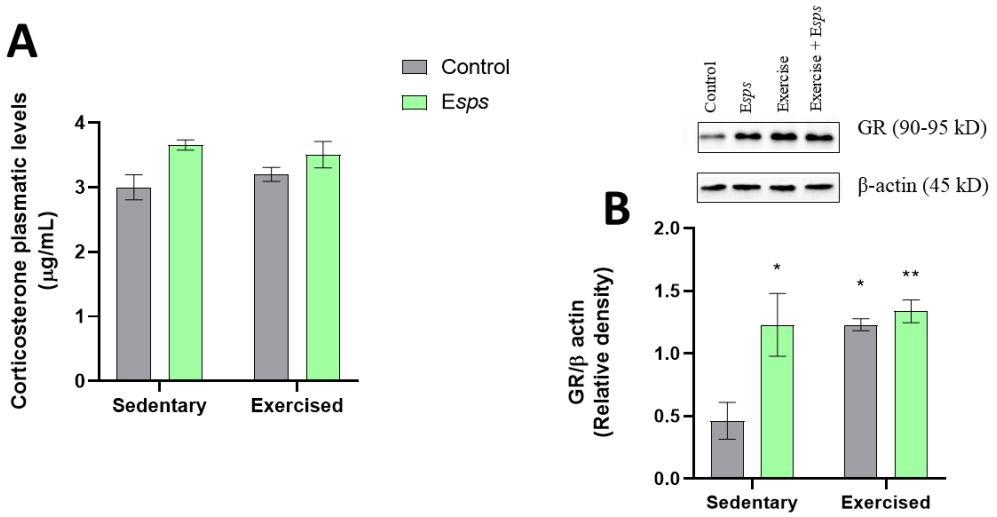


Fig. 5. Effects of resistance exercise on plasma corticosterone levels (A) and GR levels on the hippocampus (B) of mice exposed to an E*sps* protocol. Results represent the mean ± S.E.M. of 8 (A) or 5 (B) mice per group. Data were analyzed by Two-way ANOVA followed by Tukey's post-hoc test.* P<0.05; **P<0.01 compared to sedentary control group. E*sps*, emotion single prolonged stress; GR, glucocorticoid receptor.

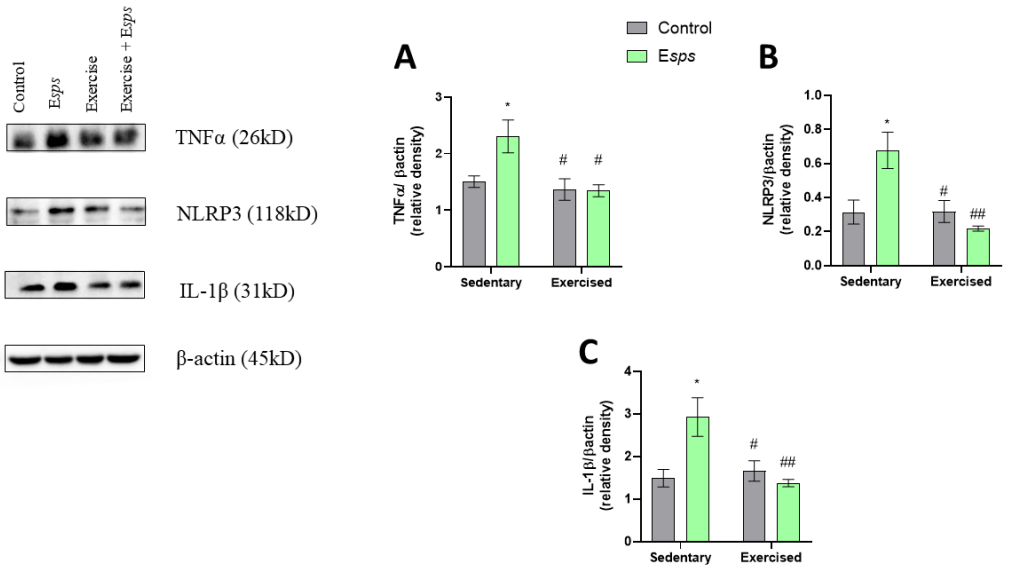


Fig. 6. Effects of resistance exercise in levels of TNFα (A), NLRP3 (B), and IL-1β (C) in the hippocampus of mice exposed to an E*sps* protocol. Results represent the mean ± S.E.M. of 5 mice per group. Data were analyzed by Two-way ANOVA followed by Tukey's post-hoc test.

* P<0.05 when compared to sedentary control; #P<0.05; ##P<0.01 when compared to sedentary E*sps* group. E*sps*, emotion single prolonged stress; TNFα, Tumor Necrosis Factor-alpha; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; IL-1β, interleukin 1-beta.

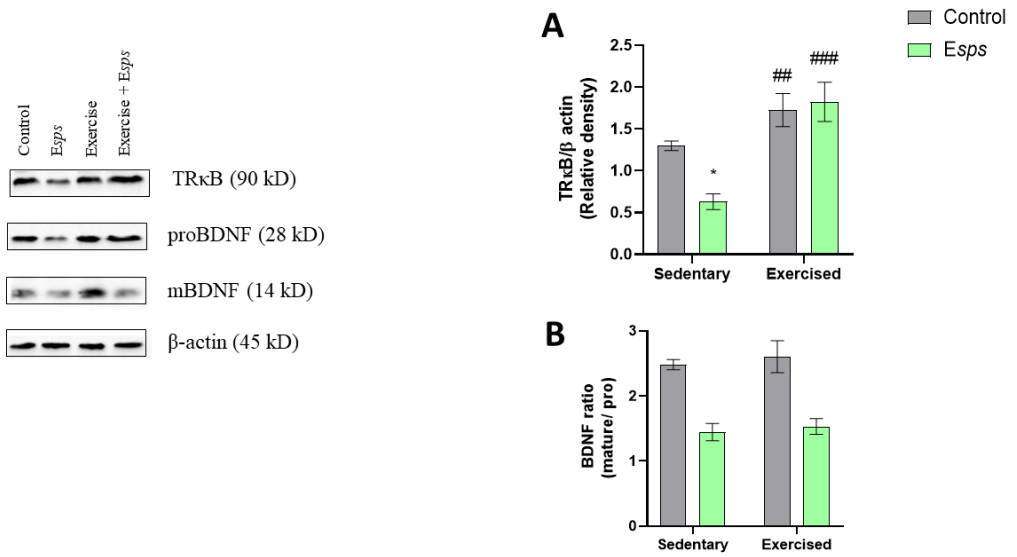


Fig. 7. Effects of resistance exercise on TRκB levels (A) and the BDNF ratio (B) in the hippocampus of mice exposed to an E*sps* protocol. Results represent the mean ± S.E.M. of 5 mice per group. Data were analyzed by Two-way ANOVA followed by Tukey's post-hoc test. * P<0.05 when compared to sedentary control; ##P<0.01; ###P<0.001 when compared to sedentary E*sps* group. E*sps*, emotion single prolonged stress; TRκB, tropomyosin-related kinase receptor; BDNF, brain-derived neurotrophic factor.

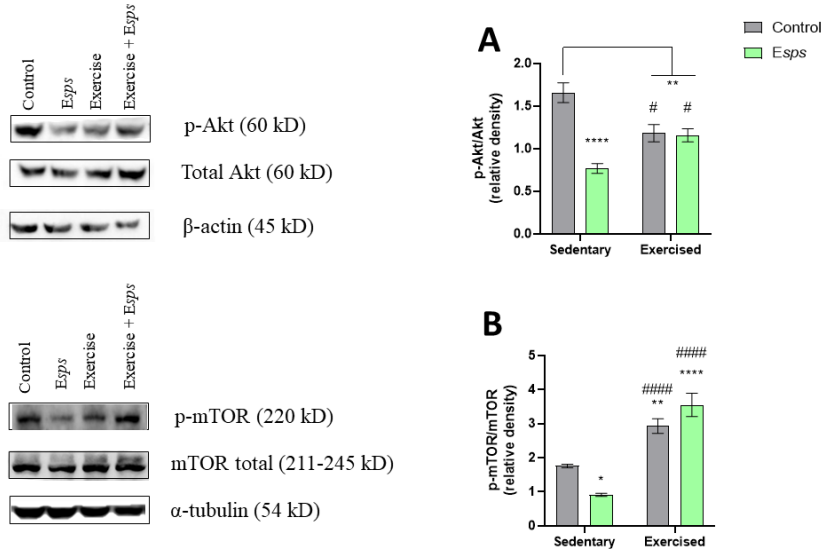


Fig. 8. Effects of resistance exercise on Akt/mTOR pathway in the hippocampus of mice exposed to an E*sps* protocol. Results represent the mean ± S.E.M. of 5 mice per group. Data were analyzed by Two-way ANOVA followed by Tukey's post-hoc test.* P<0.05; **P<0.01; ****P<0.0001 when compared to sedentary control group; #P<0.05; ####P<0.0001 when compared to sedentary E*sps* group. E*sps*, emotion single prolonged stress; Akt, protein kinase B; mTOR, mammalian target of rapamycin.

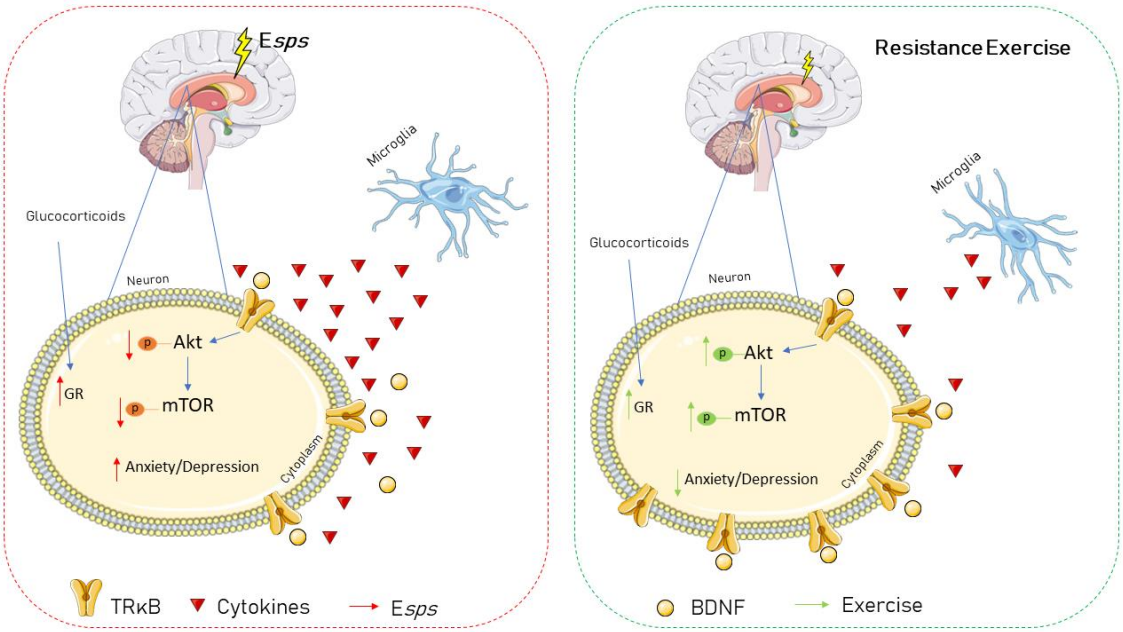


Fig. 9. Summary of E*sps* effects (red arrows) and resistance exercise (green arrows) on neuroinflammation and Akt/mTOR pathway and its signaling in the hippocampus of mice exposed to an E*sps* protocol. E*sps*, emotion single prolonged stress; GR, glucocorticoid receptor; TRκB, tropomyosin-related kinase receptor; BDNF, brain-derived neurotrophic factor; Akt, protein kinase B; mTOR, mammalian target of rapamycin.

SUPLEMENTARY MATERIAL

Resistance Training Modulates Hippocampal Neuroinflammation and Protects Anxiety-Depression-like Dyad Induced by an Emotional Single Prolonged Stress Model

Juliano Ten Kathen Jung[1], Luiza Souza Marques[1], Vanessa Angonesi Zborowski[1] Cristina Wayne Nogueira[1], Gilson Zeni*[1]

Table 1S List of primary antibodies**.**

Antibody	Type	Company	Dilution
β-actin	mouse	Sigma	1:5000
α-tubulin	mouse	Abcam	1:5000
TNFα	mouse	Santa Cruz	1:1000
TRκB	rabbit	CellSignaling	1:1000
GR	rabbit	Santa Cruz	1:1000
IL-1β	mouse	Santa Cruz	1:500
Akt1	mouse	Santa Cruz	1:1000
p-Akt	mouse	Santa Cruz	1:1000
NLRP3	rabbit	BosterBio	1:1000
BDNF	rabbit	Abcam	1:1000
mTOR	mouse	Santa Cruz	1:1000
p-mTOR	mouse	Santa Cruz	1:1000

TNFα (Tumoral necrose factor α); TrkB (tyrosine receptor kinase B), GR (Glucocorticoid receptor); IL-1β (Interleukine-1β); Akt (protein kinase B); NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3); BDNF (brain-derived neurotrophic factor); mTOR (mammalian target of rapamycin).

Table 2S Resistance Exercise effects on male mice

Parameter	Variables two-way ANOVA RM	SS	DF	MS	F	p value
Body Weight	Groups factor	236.3	1	236.3	7.486	0.0103
	Days factor	749.6	5	149.9	98.20	<0.0001
	Groups x Days	128.9	5	25.78	16.89	<0.0001
Triceps surae Weight	Groups factor	0.00025	1	0.00025	42.22	<0.0001
	Days factor	1.18e-005	1	1.18e-005	1.989	0.1695
	Groups x Days	1.71e-005	1	1.71e-005	2.817	0.1009
Parameter	Variable one-way ANOVA RM	SS	DF	MS	F	p value
MCC	Days factor	9.245	2	4622	38.43	<0.0001

Data were analyzed through two-way ANOVA repeated measures (Body weight) or one-way ANOVA repeated measures (MCC) followed by the Tukey's post-hoc test. RM means repeated-measures.

Table 3S Resistance Exercise effects on behavior tests on anxious/depressed-like male mice .

Locomotor Profile	Variables two-way ANOVA	SS	DF	MS	F	p value
Crossings	RE factor	66.7	1	66.7	0.374	0.5457
	Stress factor	2.42	1	2.42	0.013	0.9081
	RE x stress	378.1	1	378.1	2.121	0.1564
Rearings	RE factor	58.43	1	58.43	2.010	0.1673
	Stress factor	5.848	1	5.848	0.201	0.6572
	RE x stress	83.08	1	83.08	2.858	0.1020
Distance	RE factor	0.035	1	0.035	0.0071	0.9333
	Stress factor	0.047	1	0.047	0.0095	0.9229
	RE x stress	14.64	1	14.64	2.91	0.0990
Parameter	Variables two-way ANOVA	SS	DF	MS	F	p value
TST Latency	RE factor	1.791	1	1.791	0.015	0.9019
	Stress factor	113.7	1	113.7	0.983	0.3298
	RE x stress	2315	1	2315	20.02	0.0001
TST	RE factor	7332	1	7332	30.81	<0.0001
	Stress factor	3769	1	3769	15.84	0.0004
	RE x stress	2704	1	2704	11.36	0.0022
FST Latency	RE factor	448.8	1	448.8	0.965	0.3339
	Stress factor	16236	1	16236	34.93	<0.0001
	RE x stress	14345	1	14345	30.86	<0.0001
FST	RE factor	17841	1	17841	9.616	0.0044
	Stress factor	40408	1	40408	21.78	<0.0001
	RE x stress	17631	1	17631	9.503	0.0046
Splash Test Latency	RE factor	1862	1	1862	7.969	0.0087
	Stress factor	888.3	1	888.3	3.802	0.0613
	RE x stress	1206	1	1206	5.160	0.0310
Splash Test	RE factor	2086	1	2086	2.288	0.1416
	Stress factor	139.4	1	139.4	0.152	0.6987
	RE x stress	13259	1	13259	14.54	0.0007
OAT%	RE factor	1513	1	1513	25.92	<0.0001
	Stress factor	229.2	1	229.2	3.926	0.0574
	RE x stress	741.3	1	741.3	12.7	0.0013
OAE%	RE factor	465.8	1	465.8	20.29	0.0001
	Stress factor	235.7	1	235.7	10.26	0.0034
	RE x stress	347.7	1	347.7	15.14	0.0006
Anxiety Index	RE factor	0.099	1	0.099	27.00	<0.0001
	Stress factor	0.011	1	0.011	3.166	0.0860
	RE x stress	0.051	1	0.051	13.97	0.0008

Data were analyzed through two-way ANOVA followed by the Tukey's test. TST (tail suspension test, FST (forced swim test); OAT% (open-arms time); OAE% (open-arms entries); RE (resistance exercise).

Table 4S RE effects on plasma and hippocampal parameters on anxious/depressed-like male mice

Parameter	Variables two-way ANOVA	SS	DF	MS	F	p value
Corticosterone	RE factor	0.004	1	0.004	0.0247	0.8761
	Stress factor	1.85	1	1.85	9.440	0.0047
	RE x stress	0.248	1	0.248	1.269	0.2696
TNFα levels	RE factor	1.504	1	1.504	8.50	0.0101
	Stress factor	0.756	1	0.756	4.27	0.0553
	RE x stress	0.845	1	0.845	4.77	0.0440
NLRP3 levels	RE factor	0.2598	1	0.2598	9.965	0.0061
	Stress factor	0.086	1	0.086	3.325	0.0870
	RE x stress	0.267	1	0.267	10.26	0.0055
IL-1β levels	RE factor	2.392	1	2.392	6.060	0.0256
	Stress factor	1.654	1	1.654	4.191	0.0574
	RE x stress	3.684	1	3.684	9.334	0.0076
TRκB levels	RE factor	3.289	1	3.289	24.69	0.0001
	Stress factor	0.405	1	0.405	3.044	0.1002
	RE x stress	0.733	1	0.733	5.504	0.0322
BDNF levels	RE factor	0.054	1	0.054	0.441	0.5159
	Stress factor	5.568	1	5.568	45.06	<0.0001
	RE x stress	0.001	1	0.001	0.013	0.9096
Akt levels	RE factor	0.008	1	0.008	0.215	0.6485
	Stress factor	1.045	1	1.045	25.17	0.0001
	RE x stress	0.935	1	0.935	22.54	0.0002
mTOR levels	RE factor	18.17	1	18.17	86.13	<0.0001
	Stress factor	0.066	1	0.066	0.317	0.5812
	RE x stress	2.706	1	2.706	12.83	0.0025

Data were analyzed through two-way ANOVA followed by the Tukey's test.

4. CONCLUSÃO

Os resultados apresentados nesta dissertação indicam que o exercício de força é efetivo em prevenir o desenvolvimento de comportamentos do tipo ansioso e depressivo (i), neuroinflamação (ii), modular GR (iii) e modular a via Akt/mTOR (iv) em hipocampo de camundongos machos submetidos a um protocolo de estresse.

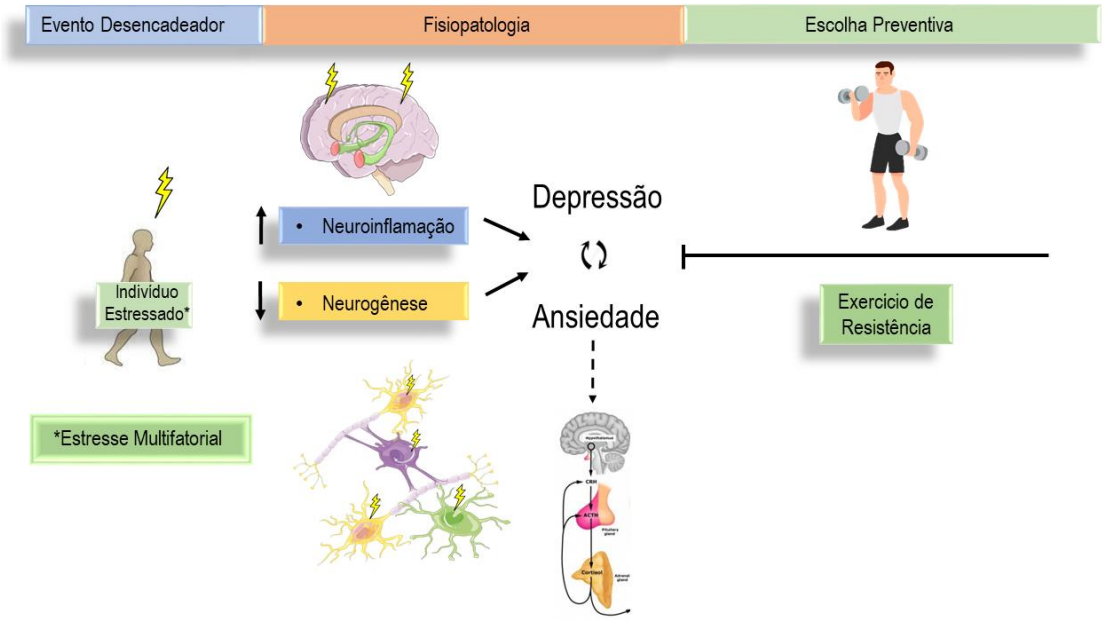
(i) O exercício de força mostrou proteger das alterações comportamentais causadas pelo estresse em parâmetros de comportamento do tipo ansioso (labririnto em cruz elevado) e depressivo (teste no nado forçado e teste de suspensão da cauda) e não causou alterações no perfil locomotor dos animais;

(ii) O exercício de força modulou citocinas pró inflamatórias (IL-1β e TNFα) no hipocampo de camundongos, além da modulação do NLRP3 na mesma estrutura, mostrando um efeito preventivo frente a neuroinflamação hipocampal.

(iii) O aumento dos níveis de GR hipocampal foi observado neste estudo, mostrando que este aumento não interfere nos efeitos benéficos do mesmo frente ao desenvolvimento da díade ansiedade/depressão em animais expostos ao estresse.

(iv) Por fim, o exercício modula a via Akt/mTOR, que pode estar relacionada aos efeitos de prevenção do desenvolvimento da díade ansiedade/depressão em camundongos machos expostos ao estresse.

Figura 5: Resumo gráfico desta dissertação.



Fonte: O próprio autor.

5. PERSPECTIVAS

A seguir, as perspectivas para trabalhos futuros:

- Elucidar as alterações do protocolo de estresse descrito em um período maior de tempo e as alterações causadas a nível central.
- Comparar os efeitos do exercício de força nas estruturas centrais córtex e hipocampo.
- Evidenciar o papel das “exercínas”, como a irisina, e seu envolvimento na fisiopatologia da díade ansiedade/depressão.
- Propor alternativas terapêuticas, em forma de moléculas orgânicas de selênio e avaliar seu comportamento a nível central.
- Avaliar outras vias associadas com a neuroinflamação, como a ativação de NF-κB.
- Avaliar outros processos celulares, como proteínas relacionadas a apoptose e autofagia no modelo utilizado.

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ANEXO A – CARTA DE APROVAÇÃO DO PROJETO DE PESQUISA PELA COMISSÃO DE ÉTICA NO USO DE ANIMAIS DA UNIVERSIDADE FEDERAL DE SANTA MARIA

Comissão de Ética no Uso de Animais
da
Universidade Federal de Santa Maria

CERTIFICADO

Certificamos que a proposta intitulada "Avaliação do tratamento com p-clorodifenil disseleneto (p-ClPhSe)2 e do exercício físico de resistência nos prejuízos comportamentais relacionados com memória/depressão em camundongos submetidos ao estresse", protocolada sob o CEUA nº 1535120320 (ID 003022), sob a responsabilidade de **Cristina Wayne Nogueira** *e equipe; Vanessa Angonesi Zborowski; Juliano Ten Kathen Jung; Luiza Souza Marques* - que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto o homem), para fins de pesquisa científica ou ensino - está de acordo com os preceitos da Lei 11.794 de 8 de outubro de 2008, com o Decreto 6.899 de 15 de julho de 2009, bem como com as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), e foi **aprovada** pela Comissão de Ética no Uso de Animais da Universidade Federal de Santa Maria (CEUA da UFSM) na reunião de 19/05/2020.

We certify that the proposal "Investigation of p-chlorodiphenyl diselenide (p-ClPhSe)2 and resistance exercise effects on memory/depression-related behavioral impairment in stressed mice", utilizing 44 Heterogenics mice (44 males), protocol number CEUA 1535120320 (ID 003022), under the responsibility of **Cristina Wayne Nogueira** *and team; Vanessa Angonesi Zborowski; Juliano Ten Kathen Jung; Luiza Souza Marques* - which involves the production, maintenance and/or use of animals belonging to the phylum Chordata, subphylum Vertebrata (except human beings), for scientific research purposes or teaching - is in accordance with Law 11.794 of October 8, 2008, Decree 6899 of July 15, 2009, as well as with the rules issued by the National Council for Control of Animal Experimentation (CONCEA), and was **approved** by the Ethic Committee on Animal Use of the Federal University of Santa Maria (CEUA da UFSM) in the meeting of 05/19/2020.

Finalidade da Proposta: Pesquisa

Vigência da Proposta: de 04/2020 a 04/2021 Área: Departamento de Bioquímica E Biologia Molecular

Origem:	Biotério Central UFSM						
Espécie:	Camundongos heterogênicos	sexo:	Machos	idade:	55 a 60 dias	N:	44
Linhagem:	Swiss			Peso:	30 a 35 g		

Local do experimento: Sala 2424- Prédio 18 e Sala 3209- Prédio 19. Durante todo o curto período em que os animais estarão em nossa sala de experimentação laboratorial, a limpeza e a troca das palhas de cada uma das caixas serão efetuadas por um funcionário, que está devidamente treinado para realizar estes procedimentos, causando o mínimo possível de desconforto para os animais experimentais. O transporte dos animais ao local adequado para as atividades experimentais seguirá os seguintes cuidados: I- O transporte será realizado, preferencialmente, antes das 10h da manhã. Evitando o transporte nos horários de pico de temperatura e tráfego intenso; II- Os animais serão levados diretamente até seu destino final, a fim de minimizar o estresse a que serão submetidos neste momento; III - Os animais serão acondicionados em caixas apropriadas para o transporte, as quais permitam que se movimentem confortavelmente e proporcionem travamento adequado para impedir fugas, garantindo a segurança destes, do usuário e do meio ambiente; IV- As caixas de transporte serão previamente higienizadas e preparadas com cama apropriada, bem como estarão devidamente identificadas. V- Por questões de segurança a caixa de transporte estará sempre coberta com material que permita ventilação e impeça que os animais possam ser observados durante o percurso; VI- Antes do transporte os bebedouros serão retirados para evitar vazamentos.

Santa Maria, 17 de fevereiro de 2022

Dra. Patrícia Bräunig
Presidente da Comissão de Ética no Uso de Animais
Universidade Federal de Santa Maria

Profa. Dra. Vania Lucia Loro
Vice-Presidente da Comissão de Ética no Uso de Animais
Universidade Federal de Santa Maria

Avenida Roraima, 1000, Reitoria, 7º andar, sala 763 - CEP 97105-900 Santa Maria, RS - tel: 55 (55) 3220-9362
Horário de atendimento: 8h30 - 11h30 e 13h30 - 16h30 : e-mail: ceua.ufsm@gmail.com
CEUA N 1535120320