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**AVALIAÇÃO DA INFLUÊNCIA DO EXERCÍCIO FÍSICO VOLUNTÁRIO NA
NEUROGÊNESE E NA PLASTICIDADE SINÁPTICA NA PROLE DE
CAMUNDONGOS COM DELEÇÃO CONDICIONADA DA PTEN**

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Resumo

Andreotti-Viana, D.Z. Avaliação da influência do exercício físico voluntário na neurogênese e na plasticidade sináptica na prole de camundongos com deleção condicionada da PTEN. [Tese de Doutorado em Farmacologia] – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo; 2018.

O gene da PTEN (Phosphatase and tensin homolog on chromosome ten) foi primeiramente estudado como um gene supressor de tumor. No entanto, devido as características abrangentes desta fosfatase que podem influenciar a proliferação, sobrevivência e migração celular, a PTEN também parece estar envolvida nos fenômenos da neurogênese e plasticidade sináptica.

Estudos sugerem que não somente fatores genéticos, mas também ambientais podem influenciar o processo de neurogênese. Entender os mecanismos pelos quais isso ocorre pode trazer benefícios no tratamento ou até mesmo na prevenção de doenças relacionadas ao sistema nervoso central (SNC). Como exemplo, o exercício físico tem demonstrado exercer efeitos benéficos em processos associados ao envelhecimento e a doenças neurodegenerativas. A prática de exercício físico durante a gestação também pode favorecer a neurogênese e a plasticidade sináptica na prole, e esses efeitos benéficos podem perdurar até a idade adulta desses animais.

Portanto, este projeto teve como escopo avaliar os efeitos do exercício físico voluntário na neurogênese e na plasticidade sináptica em animais com a deleção parcial do gene da PTEN. Foram observadas alterações positivas quanto ao aprendizado da prole com a deleção condicionada da PTEN durante o aprendizado da tarefa do Labirinto Aquático de Morris, além do aumento de marcadores moleculares relacionados ao fenômeno da plasticidade sináptica da subunidade NR1 do receptor glutamatérgico nesses animais e o aumento da do fator neurotrófico derivado do cérebro.

De forma geral o exercício físico materno foi capaz de aumentar alguns marcadores relacionados ao fenômeno da plasticidade sináptica, envolvido diretamente na formação de memória e da capacidade de aprendizado. Portanto, os resultados sugerem que o exercício físico materno, desde que

respeitada as condições do cuidado materno durante o puerpério e a amamentação, pode ser benéfico para a prole *wild type* e com a deleção parcial da PTEN.

Palavras-chaves: PTEN, exercício físico voluntário, cognição, intervenções não-farmacológicas.

Abstract

Andreotti-Viana, D.Z. Evaluation of the influence of voluntary physical exercise on neurogenesis and synaptic plasticity in offspring of conditioned PTEN deletion. [ph.D thesis in Pharmacology] – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo; 2018.

PTEN was first studied as a tumor suppressor gene. However, due to the comprehensive characteristics of this phosphatase that can influence cell proliferation, survival and migration, PTEN may be also involved in the neurogenesis and synaptic plasticity.

Studies suggest that not only genetic but also environmental factors can influence the process of neurogenesis. Understanding the mechanisms by which this occurs can bring benefits in the treatment or even the prevention of diseases related to the central nervous system (CNS). As an example, physical exercise has been shown to exert beneficial effects in processes associated with aging and neurodegenerative diseases. The practice of physical exercise during pregnancy seem also favor neurogenesis and synaptic plasticity in the offspring, and these beneficial effects may last until the adulthood of these animals.

Therefore, the purpose of this project was to evaluate the effects of voluntary physical exercise on neurogenesis and synaptic plasticity in animals with partial deletion of PTEN gene. Positive alterations were observed regarding offspring learning with the conditional PTEN deletion during the learning of the Morris water maze task, as well as the increase of the subunit N-Methyl-D-Aspartate receptor 1 (NR1) in these animals and an increase in brain derived neurotrophic factor levels.

In general, maternal physical exercise was able to increase some markers related to the phenomenon of synaptic plasticity, directly involved in the formation of memory and learning capacity. Therefore, the results suggest that maternal physical exercise, while respecting the conditions of maternal care during the puerperium and breastfeeding, may be beneficial to the wild type offspring and with the partial deletion of PTEN.

Key words: PTEN, voluntary physical exercise, cognition, non-pharmacological interventions.

1. Introdução

Descoberta primeiramente como um gene supressor de tumor, a PTEN vem sendo associada a doenças relacionadas ao déficit cognitivo, como a doença do espectro do autismo, sendo utilizado como modelo para estudos desta desordem neuropsiquiátrica. Dados da literatura descritos no item 1 e resultados prévios do grupo do Laboratório de Neurobiologia Molecular e Funcional destacam a importância da PTEN na modulação da plasticidade sináptica no hipocampo e no córtex e da neurogênese, em especial na região do giro dentado. Amplamente explorado na literatura, sabe-se também dos benefícios do exercício físico para o aumento da neurogênese e formação de memória, através do estímulo de fatores de crescimento, como o BDNF, e esses estímulos podem ser transmitidos para a prole desses animais, através da prática de exercício físico durante a prenhez.

Levando em consideração a função do hipocampo e do córtex nas atividades cognitivas, bem como na formação de memória e aprendizado, este projeto teve como objetivo principal caracterizar a função da PTEN e sua interação com os efeitos mediados pelo exercício físico, avaliando a via da PI3K/AKT e os efeitos comportamentais relacionados ao aprendizado e à memória na prole e nas progenitoras do modelo de camundongos *Pten*^{loxp/+}; *Nse-Cre*⁺ submetidos ao exercício físico voluntário. Desse modo, pode-se contribuir com alternativas para amenizar os sintomas provocados por doenças que tem relação com a supressão do gene da PTEN, além de uma melhor elucidação da ação fisiológica da PTEN sob a influência de fatores ambientais.

uma forma de compensação no aumento do CREB provocado pela deleção da PTEN (figuras 46 e 47).

7. Conclusão

De forma geral o exercício físico materno foi capaz de aumentar alguns marcadores relacionados ao fenômeno da plasticidade sináptica, envolvido diretamente na formação de memória e da capacidade de aprendizado, corroborado com uma melhor performance em alguns testes comportamentais. Portanto, os resultados sugerem que o exercício físico materno, desde que respeitada as condições do cuidado materno durante o puerpério e a amamentação, pode ser benéfico para a prole *wild type*, e HT para o gene da PTEN. Quanto as progenitoras, concluímos que o exercício voluntário com uma duração mais prolongada pode apresentar benefícios diretos nessas fêmeas, como o aumento da expressão de marcadores relacionados à plasticidade sináptica.

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