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INSTITUTO DE BIOCIÊNCIAS DE BOTUCATU

Exposição ao antidepressivo sertralina associado ou não ao estresse/ou probiótico em diferentes períodos do desenvolvimento: Uma abordagem sobre os impactos reprodutivos e neurocomportamentais em roedores

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Tese apresentada ao Instituto de Biociências, Campus de Botucatu, UNESP, para obtenção do título de Doutora no Programa de Pós-Graduação em Biologia Geral e Aplicada, área de concentração Biologia Celular, Estrutural e Funcional.

Orientadora: Profa. Dra. Wilma De Grava Kempinas

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Sumário

Dedicatória

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"Nenhuma árvore alcança os céus sem a força de suas raízes"

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"Cada pessoa que passa em nossa vida, passa sozinha, é porque cada pessoa é única e nenhuma substitui a outra! Cada pessoa que passa em nossa vida passa sozinha e não nos deixa só porque deixa um pouco de si e leva um pouquinho de nós. Essa é a mais bela responsabilidade da vida e a prova de que as pessoas não se encontram por acaso".

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Epígrafe

"No caminho aprendemos, no caminho florescemos, no caminho nos tornamos. Nos tornamos quando mudamos de acordo com as evoluções que a vida nos permite experenciar. Nos tornamos quando aprendemos a ser mais gentis, mais flexíveis e corajosos para surfar as ondas gigantes da vida. É sobre aprender a fazer o melhor que puder, com o que tiver, aonde estiver. É sobre ser gentil com as nossas limitações. É sobre entender que haverá luz e haverá escuridão, e aprender a se equilibrar entre estes extremos é tudo o que podemos fazer. Tornar-se é sobre ser um pouco mais de nós a cada dia. Ouvindo, respeitando e seguindo a nossa intuição, os nossos sentimentos, os nossos instintos. Tornar-se é sobre a marca que deixamos em cada coração que tocamos e cada pessoa que encontramos."

Wandy Luz

Resumo

A depressão, o estresse e a ansiedade são comumente observados na população, e como consequência o consumo de antidepressivos tem aumentado exponencialmente nos últimos anos. A sertralina (SE), classificada como inibidor seletivo de recaptação de serotonina (ISRS), é um antidepressivo/ansiolítico utilizado por pessoas com distintos transtornos psiquiátricos e diferentes faixas etárias. Os ISRS podem provocar graves efeitos colaterais, no entanto existem poucos relatos sobre os impactos da SE em aspectos reprodutivos e comportamentais, tampouco há tratamentos adjuvantes que amenizem seus efeitos indesejáveis. Sabendo-se dos benefícios dos probióticos no eixo microbiota-intestino-cérebro e sua ação benéfica na saúde reprodutiva, o presente estudo investigou os impactos da exposição à SE associada ou não ao estresse/ ou probiótico, em diferentes períodos do desenvolvimento de roedores. Testes estatísticos utilizados: ANOVA (seguido pelo teste de Tukey) ou Kruskal-Wallis (seguido pelo teste de Dunn) ($p \leq 0.05$). Para o experimento I e II, ratas Wistar prenhes foram distribuídas nos grupos (n=20-18 ratas/grupo): CO - receberam água filtrada; SE – receberam 20 mg/kg de SE; ST - animais submetidos ao estresse por contenção e receberam água filtrada; ST/SE - animais submetidos ao estresse e receberam 20 mg/kg de SE. O tratamento foi realizado por via gavagem entre os dias gestacionais (DG) 13 ao 20. Parte das fêmeas prenhes foram eutanasiadas no DG 20 para análise dos fetos, e o restante foi mantida até o final da lactação. No experimento I, a maturação somática, o desenvolvimento de reflexos, e o neurocomportamento foram investigados na prole masculina. No experimento II, foram analisados no DG 20, e nos dias pós-natais (DPN) 21, 45 e 110, a histologia dos testículos e epidídimos, bem como a imuno-histoquímica testicular do antígeno nuclear de proliferação celular (PCNA) e proteína do tumor de Wilms (Wt1). A morfologia, motilidade e vitalidade espermáticas foram observadas no DPN 110, assim como a produção diária de espermatozoides e seu tempo de trânsito epididimário. Os resultados do experimento I mostraram que a exposição gestacional à SE provocou redução do peso corporal e sangramento vaginal nas mães. Já a prole masculina do grupo SE apresentou atrasos na erupção dos incisivos, no aparecimento de pelos e na realização de geotaxia negativa. Além disso, o grupo SE foi menos exploratório (personalidade ansiosa) em comparação com os grupos CO e ST. No experimento II, observou-se que os testículos fetais apresentaram grande número de células acidófilas, que representam células em processo de morte celular, nos grupos expostos à SE. O grupo ST/SE também apresentou diminuição do volume nuclear das células de Leydig. Este mesmo grupo mostrou baixa expressão de PCNA e WT1, diminuição do peso dos testículos e epidídimo, menor distância anogenital (DAG) e atraso na instalação da puberdade. Os animais adultos, expostos *in útero* à SE apresentaram alterações na morfologia e motilidade espermática. O experimento III foi conduzido de forma a investigar as repercussões reprodutivas e comportamentais da exposição lactacional à SE. Para tanto, 30 ratas Wistar lactantes foram distribuídas em 3 grupos experimentais (n=10/grupo): grupo CO- recebeu água filtrada, grupos S10 e S20 receberam, respectivamente, 10 e 20 mg/kg/dia de SE. O tratamento foi realizado por via gavagem do 1º ao 20º dia de lactação. Nesse período, observou-se o desenvolvimento de reflexos e somáticos da prole masculina, bem como o comportamento materno. No dia 21, as mães foram eutanasiadas, e nos dias 21, 45 e 100, um macho de cada ninhada foi eutanasiado. Além das metodologias realizadas no experimento I e II, também foram observados o comportamento sexual e fertilidade natural. Os resultados mostraram que a prole masculina exposta à SE apresentou menor peso corporal, menor DAG e alterações no desenvolvimento dos reflexos, além de alterações histológicas nos testículos. Na idade adulta, a maioria dos parâmetros analisados foram normalizados, porém, a qualidade espermática mostrou-se alterada, sem comprometimento da fertilidade natural. O experimento IV investigou os efeitos da SE nos parâmetros reprodutivos de camundongos adultos, bem como verificou se o probiótico *Lactobacillus rhamnosus* (Lr) reduz os efeitos colaterais desse

antidepressivo. Assim, duas etapas consecutivas foram desenvolvidas. Na 1ª etapa, quatro grupos experimentais (n=6/grupo) foram formados: Grupo CO recebeu água filtrada (veículo); e grupos S10, S20 e S40 receberam respectivamente 10, 20 e 40 mg/Kg de SE diluída em veículo. O tratamento ocorreu via gavagem por 30 dias. Ao final do tratamento, foram analisados a qualidade espermática, o peso de órgãos e a histologia dos testículos e epidídimos. Na 2ª etapa, 32 camundongos foram distribuídos em 4 grupos experimentais (n=8/grupo): Grupo CO recebeu água filtrada (veículo); grupo S –recebeu 20 mg/Kg de SE; grupo P- recebeu o probiótico Lr (1×10^9 UFC), diluído em veículo; e grupo SP que recebeu tanto LR quanto SE. Ao final do tratamento, por via gavagem, foram analisadas a histologia dos testículos e epidídimos, qualidade espermática, verificação da fertilidade natural. De forma complementar, ensaio *in vitro* foram realizados com o intuito de identificar os efeitos da SE sobre a reação acrossômica durante a capacitação e fertilização *in vitro*. Os resultados da 1ª etapa demonstraram que os animais dos grupos S10 e S20 apresentaram diminuição do peso das glândulas seminais em relação ao grupo CO ($p<0.05$). Na 2ª etapa, observou-se que o grupo S também teve uma menor glândula seminal. Esta, no grupo SP, manteve-se com peso semelhante ao grupo CO. Embora um atraso no tempo de trânsito espermático tenha sido observado no grupo SP, a fertilidade natural não foi comprometida. Além disso, esse mesmo grupo apresentou maior número de fetos e menor número de reabsorções comparado ao grupo S ($p<0.05$). Nos testes neurocomportamentais, observou-se que os perfis dos animais dos grupos P e S foram diferentes entre si ($p<0.05$), sendo este último menos exploratório e mais ansioso. Assim, os quatro experimentos aqui desenvolvidos demonstram que a SE tem impacto no sistema reprodutor e no neurocomportamento de roedores em diferentes fases da vida. E pela primeira vez, demonstrou-se que o probiótico foi capaz de atenuar estes efeitos colaterais.

Abstract

Depression, stress, and anxiety are commonly observed in the population, and as a consequence, the consumption of antidepressants has increased exponentially in recent years. Sertraline (SE), classified as a selective serotonin reuptake inhibitor (SSRI), is an antidepressant/anxiolytic used by people with different psychiatric disorders and different ages. SSRIs can cause serious side effects, however, there are few reports on the impacts of SE on reproductive and behavioral aspects, nor are there adjuvant treatments that alleviate its undesirable effects. Knowing the benefits of probiotics on the microbiota-gut-brain axis and its beneficial action on reproductive health, the present study investigated the impacts of SE associated or not with stress/or probiotic, in different periods of rodent development. Statistical tests used: ANOVA (followed by Tukey's test) or Kruskal-Wallis (followed by Dunn's test) ($p \leq 0.05$). For experiment I and II, pregnant Wistar rats were distributed into groups (n=20-18 rats/group): CO - received filtered water; SE – received 20 mg/kg of SE; ST - animals subjected to restraint stress and received filtered water; ST/SE - animals submitted to stress and received 20 mg/kg of SE. The treatment was carried out by gavage between gestational days (GD) 13 to 20. Part of the pregnant females was euthanized on GD 20 for analysis of the fetuses, and the rest were maintained until the end of lactation. In experiment I, somatic maturation, reflex development, and neurobehavior were investigated in male offspring. In experiment II, on GD 20 and on postnatal days (PND) 21, 45 and 110, the histology of the testes and epididymis were analyzed, as well as the testicular immunohistochemistry of the proliferating cell nuclear antigen (PCNA) and Wilms tumor protein (Wt1). Sperm morphology, motility, and vitality were observed on PND 110, as well as daily sperm production and epididymal transit time. The results of experiment I showed that gestational exposure to SE caused a reduction in body weight and vaginal bleeding in mothers. The male offspring of the SE group showed delays in the eruption of the incisors, in fur development, and in the performance of negative geotaxis. Furthermore, the SE group was less exploratory (anxious personality) compared to the CO and ST groups. In experiment II, it was observed that the fetal testes had a large number of acidophilic cells in the groups exposed to SE. The ST/SE group also showed a decrease in the nuclear volume of Leydig cells. This same group showed low expression of PCNA and WT1, decreased weight of the testes and epididymis, shorter anogenital distance (AGD), and delayed onset of puberty. Adult animals exposed *in utero* to SE showed changes in sperm morphology and motility. Experiment III was conducted in order to investigate the reproductive and behavioral repercussions of lactational exposure to SE. For this purpose, 30 lactating Wistar rats were divided into 3 experimental groups (n=10/group): CO- group received filtered water, S10 and S20 groups received, respectively, 10 and 20 mg/kg/day of SE. The treatment was carried out by gavage from the 1st to the 20th day of lactation. During this period, the reflex and somatic development of male offspring was observed, as well as maternal behavior. On day 21, the mothers were euthanized, and on days 21, 45 and 100, one male from each litter was euthanized. In addition to the methodologies carried out in experiment I and II, sexual behavior and natural fertility were also observed. The results showed that the male offspring exposed to SE had lower body weight, lower AGD, and changes in the development of reflexes, in addition to histological alterations in the testes. In adulthood, most of the parameters analyzed were normalized, however, sperm quality was altered without compromising natural fertility. Experiment IV investigated the effects of SE on the reproductive parameters of mice, as well as verified whether the probiotic *Lactobacillus rhamnosus* (Lr) alleviates the side effects of this antidepressant. Thus, two consecutive steps were developed. In the first step, four experimental groups (n=6/group) were formed: Group CO received filtered water (vehicle); and groups S10, S20, and S40 received respectively 10, 20 and 40 mg/Kg of SE diluted in the vehicle. The treatment occurred by gavage for 30 days. At the end of treatment, sperm quality, organ weight, and histology of testes

and epididymis were analyzed. In the second step, 32 mice were distributed into 4 experimental groups (n=8/group): Group CO received filtered water (vehicle); Group S – received 20 mg/kg of SE; Group P- received the probiotic Lr (1×10^9 CFU), diluted in vehicle; and SP group that received both Lr and SE. At the end of treatment, the histology of the reproductive organs and sperm quality were analyzed. Natural fertility was also verified. Complementarily, *in vitro* tests were carried out in order to identify the effects of SE on the acrosomal reaction during capacitation and *in vitro* fertilization. The results of the the first step demonstrated that the animals in the S10 and S20 groups presented a decrease in the weight of the seminal glands in relation to the CO group ($p<0.05$). In the second step, it was also observed that the S group had a smaller seminal vesicle. This organ, in the SP group, maintained a similar weight to the CO group. Although a delay in sperm transit time was observed in the SP group, natural fertility was not compromised. Furthermore, this same group had a higher number of fetuses and a lower number of resorptions compared to the S group ($p<0.05$). In the neurobehavioral tests, it was observed that the profiles of the animals in the P and S groups were different from each other ($p<0.05$), the latter being less exploratory and more anxious. Thus, the four experiments demonstrate that SE has an impact on the reproductive system and on the neurobehavior of rodents at different life stages. And for the first time, we demonstrated that the probiotic was able to attenuate these side effects.

1- Sistema Reprodutor

O desenvolvimento dos mamíferos é caracterizado por uma série de períodos críticos, durante os quais o ambiente fetal pode influenciar a vida pós-natal. A saúde reprodutiva é determinada já na fase embrionária e a diferenciação sexual genital envolve eventos pelos quais o embrião adquire progressivamente características masculinas ou femininas (Rey *et al.*, 2000).

A constituição cromossômica, determinará o sexo genético e levará a gônada primitiva a se diferenciar em testículo ou ovário. Sob a orientação do gene SRY no cromossomo Y, a produção de testosterona resulta na regressão do trato genital feminino e no desenvolvimento dos órgãos reprodutores masculinos e na programação de um fenótipo permanente (Mäkelä *et al.*, 2019).

As células germinativas primordiais (CGP) são observadas próximas à base do alantoide em desenvolvimento na parede do saco vitelino. À medida que o embrião se dobra, a parte do endoderma extraembrionário que é habitada pelas CGP é incorporada ao embrião e forma o intestino médio e o intestino posterior. Por meio de migração e por deslocamentos causados pelos movimentos de crescimento embrionário, as CGP saem do saco vitelino e atingem as gônadas bipotenciais (Mäkelä *et al.*, 2019) (Figura 1).

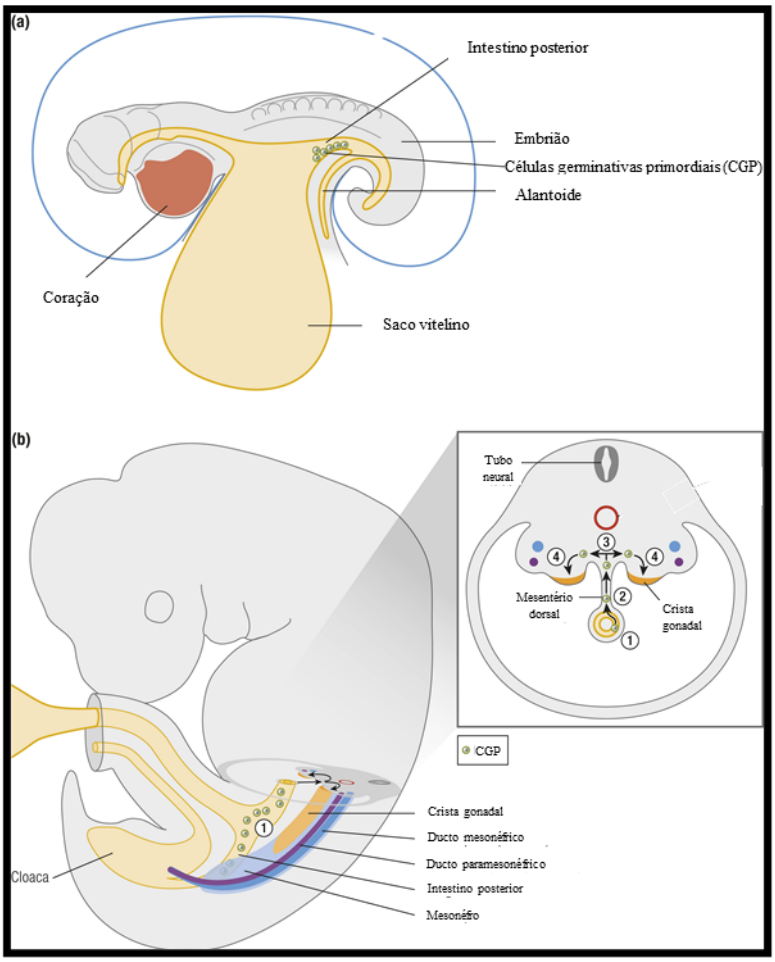

Figura 1. Formação inicial das gônadas indiferenciadas. Local inicial das células germinativas primordiais (a) e seu deslocamento (b). Etapas 1,2,3 e 4 referem-se à migração celular até a crista gonadal (Mäkelä *et al.*, 2019).

Os fatores que estão envolvidos com a diferenciação da gônada incluem o fator esteroidogênico 1 (Sf1), o supressor tumoral de Wilms (WT1) e a proteína homeobox de Lim (LHX-9). Durante a diferenciação gonadal, o WT1 é expresso no epitélio celômico e posteriormente nas células de Sertoli e granulosa. O SF1 também é um receptor nuclear expresso na hipófise e nas gônadas. O WT1, através da interação com CITED2 e LHX-9 regulam a expressão de SF1 e a montante da cascata de desenvolvimento gonadal. Fatores da família GATA4 e SOX também regulam a expressão de SF1 na gônada (Wilhelm e Englert, 2002).

Durante a diferenciação do testículo, os cordões seminíferos e o interstício são formados. As células de Sertoli originam-se a partir das células epiteliais do celoma embrionário e envolvem os gonócitos para formar os cordões seminíferos. Formam também

uma importante barreira através de junções especializadas que protegem as células germinativas e permitem a ocorrência da espermatogênese (O'Donnell *et al.*, 2022).

Os cordões dão origem aos túbulos seminíferos adultos, enquanto as células de Leydig e outros tipos celulares se diferenciam na região do interstício. Os precursores das células de Leydig fetais têm sido propostos como células migratórias do epitélio celômico, do mesonefro ou da crista neural ou células residentes presentes no primórdio adrenogonadal. Estas células produzem altos níveis de androgênio fundamental para a diferenciação da genitália masculina e masculinização do cérebro, assim como manutenção do processo de espermatogênese (Zirkin e Papadopoulos, 2018). Em ratos, as células de Leydig adultas se desenvolvem a partir de células de Leydig tronco que estão presentes no testículo pré-púbere, sendo essenciais para as funções fisiológicas do sistema reprodutor masculino (Chen *et al.*, 2017).

Dependendo da espécie analisada, os dias para o surgimento da crista genital e demais etapas do desenvolvimento reprodutivo podem ser diferentes, como observado na Figura 2.

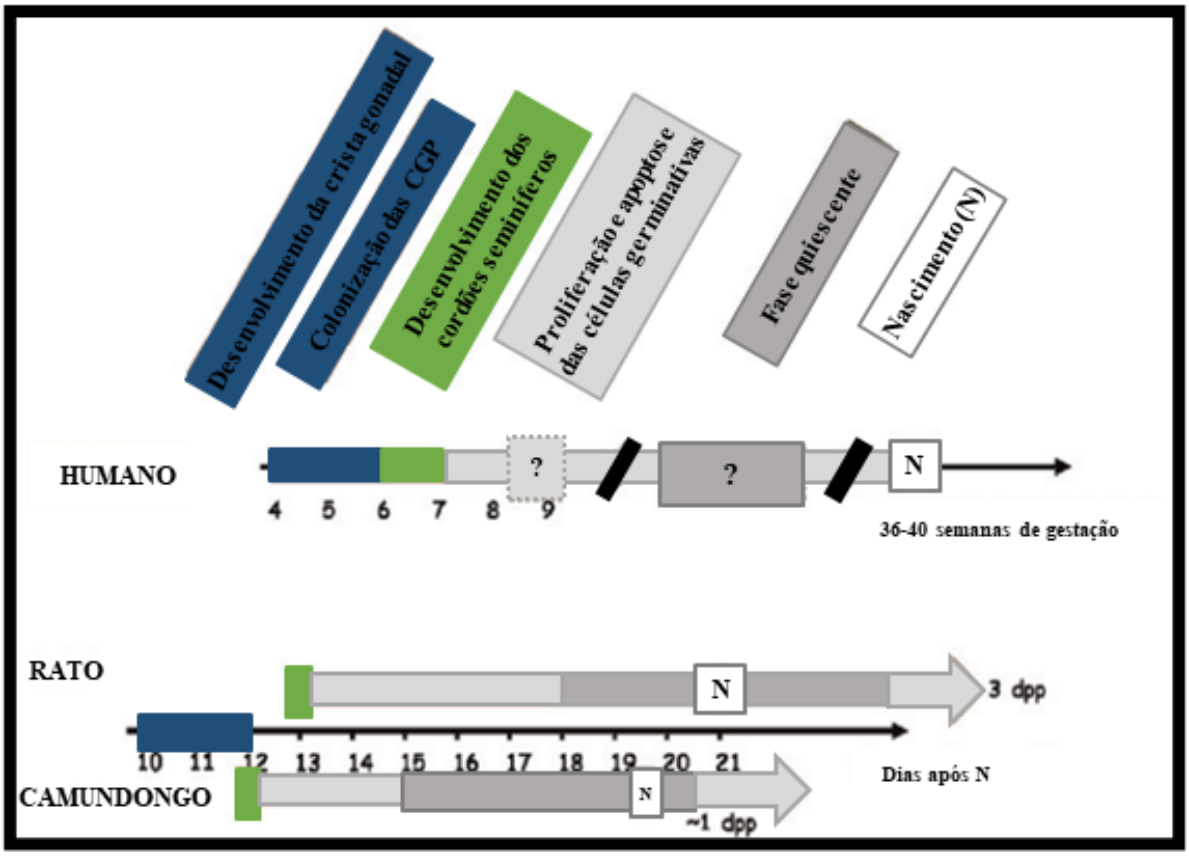

Figura 2. Cronologia comparativa do desenvolvimento de testículos fetais de humanos, ratos e camundongos (Rouiller-Fabre *et al.*, 2009).

Após o nascimento de roedores, uma subpopulação de pré-espermatogônias se diferenciam em espermatogônias indiferenciadas (tronco e progenitoras). Um outro grupo de

pré-espermatogônias diferencia-se diretamente em espermatogônias A1 e A2 e inicia o primeiro ciclo da espermatogênese. As pré-espermatogônias estão localizadas no centro do cordão seminífero e interagem com células de Sertoli imaturas (Yan *et al.*, 2020).

As espermatogônias (diploides, 2C) se desenvolvem em espermatócitos pré-leptótenos (4C) após a replicação pré-meiótica do DNA. A primeira divisão meiótica gera espermatócitos secundários que possuem duas cópias de cada gene (células 2C). Estas células sofrem a segunda divisão meiótica e originam espermátides haploides (células 1C) que se diferenciarão em espermatozoides. A duração da espermatogênese varia de espécie para espécie, em camundongos por exemplo, a duração é de 35 dias, enquanto no rato é 54 dias e no humano é 74 dias (Perrard *et al.*, 2016).

Os túbulos seminíferos convergem para formar a rete testis, que por sua vez dá origem aos ductos eferentes que convergem para formar um único ducto altamente enrolado, o epidídimo que varia de 1 m em camundongos, 3 m em ratos, e de 3 a 6 m no homem. Anatomicamente pode ser dividido em quatro regiões, o segmento inicial, a cabeça, o corpo e a cauda. Durante o trânsito espermático pelo epidídimo a capacidade fertilizante e a motilidade são adquiridas (Robaire *et al.*, 2006).

Conclusão

Os resultados demonstraram que o tratamento com SE, em diferentes períodos da vida de roedores, tem repercussões negativas em parâmetros reprodutivos e neurocomportamentais. Por sua vez, o *Lactobacillus rhamnosus* mostrou-se efetivo em atenuar estes efeitos colaterais desenvolvidos em camundongos adultos.

Assim, sob o aspecto translacional, esclarecemos à comunidade científica e médica sobre os impactos desencadeados pela SE. E também fornecemos informações importantes que podem contribuir com a compreensão dos efeitos de probióticos.

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