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**Efeitos do enriquecimento ambiental e da oxitocina sobre o consumo de etanol  
em camundongos C57BL/6 submetidos ao estresse agudo**

Dissertação apresentada ao Programa de Pós-Graduação em Farmacologia do Instituto de Ciências Biomédicas da Universidade de São Paulo, para obtenção do Título de Mestre em Ciências.

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O etanol é a droga de abuso mais consumida em todo o mundo. Frequentemente, há comorbidade entre o alcoolismo e transtornos relacionados ao estresse. O enriquecimento ambiental (EA) reduz o comportamento ansioso em resposta ao estresse e conseqüentemente minimiza os efeitos reforçadores de drogas de abuso. Como o enriquecimento induz interações sociais, deve promover a liberação de oxitocina (OT), um neuropeptídeo liberado em resposta a experiências sociais. A OT tem propriedades ansiolíticas que devem conferir proteção aos efeitos deletérios do estresse. Neste trabalho, verificamos se o EA ou a OT protegem contra o consumo de etanol em camundongos machos C57BL/6, mesmo após a exposição ao estresse de exposição ao predador, um modelo de transtorno de estresse pós traumático (TEPT). Para avaliar os efeitos do EA, os animais foram divididos entre caixas padrão (NE) e caixas enriquecidas (EA) após a fase de aquisição, onde permaneceram por 21 dias. Em seguida foram subdivididos em grupos não estressados (NENS e EANS) e estressados (NEST e EAST) e reexpostos novamente ao etanol por 24h após o estresse; após 7 dias, com avaliação do comportamento do tipo ansioso por Labirinto em Cruz Elevado; e após 14 dias do estresse, quando passaram pela Caixa Claro-Escuro. Dentre os animais estressados, EAST reduziu o consumo e exibiu menos comportamento de medo e ansiedade. Em outro experimento, verificamos os efeitos de diferentes doses de carbetocina (CBT), um análogo da OT, sobre a ingestão de álcool. Então, foi realizado o tratamento crônico com CBT em camundongos, sendo que um grupo recebeu salina (CTL), outro recebeu CBT 1h antes das reexposições (CBT1h) e o último recebeu CBT 16h antes das reexposições ao etanol (CBT16h). Os animais passaram pelo mesmo delineamento do experimento anterior. A CBT1h teve efeito protetor sobre o consumo de álcool após estresse, enquanto a CBT16h não

**Palavras-chave:** Etanol. Enriquecimento Ambiental. Oxitocina. Estresse. TEPT.

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Ethanol is the most commonly abused drug. Comorbidity between alcoholism and stress related disorders is highly frequent. Environmental enrichment (EE) reduces anxiety-like behaviour and consequently minimizes reinforcing effects of abused drugs. As EE favours social interactions, it might promote oxytocin (OT) release. OT is a neuropeptide secreted after social experiences. It is also related that OT has anxiolytic properties, which confers protection against stress maladaptive effects. The purpose of this work was to check if EE or OT protect against ethanol intake in male C57BL/6 abstinent mice even after stress exposure. To evaluate EE effects, animals were divided between standard housing (NE) and enriched housing (EA) after acquisition for 21 days. Then, both groups were subdivided into non-stressed (NENS, EANS) and stressed (NEST, EAST) and were submitted to predator exposure stress, a model of post traumatic stress disorder (PTSD). Right after stress, animals were reexposed to ethanol for 24h; after 7 days, when anxiety-like behaviour was evaluated by Elevated Plus Maze; and after 14 days of stress, when their behaviour was assessed by Light Dark Box. Among stressed animals, EAST reduced ethanol intake and exhibited decreased anxiety-like behaviour and fear. We determined the effects of different doses of carbetocin (CBT) on alcohol intake. In another experiment, mice were chronically treated CBT, an OT analogue. Control mice received saline (CTL), CBT1h were treated 1 hour before ethanol reexposure and CBT16h were treated 16 hours before reexposures. The protocol was the same of the first experiment. CBT1h protected against ethanol intake after stress, while CBT16h did not. These results show that EE buffers ethanol. CBT reduced ethanol consumption when it was administered immediately before stress.

**Keywords:** Ethanol. Environmental enrichment. Oxytocin. Stress. PTSD.

## 1 INTRODUÇÃO

O consumo de etanol é bastante comum em nossa sociedade e muitas são as razões pelas quais a população engaja neste comportamento. Muitas pessoas relatam sensações de prazer com o álcool e bebem por divertimento; outros são influenciados pelos amigos e consomem para se sentirem incluídos em grupos sociais. Ainda existem aqueles que bebem para se sentirem menos tensos em situações de estresse, já que os efeitos iniciais do consumo incluem desinibição (KOOB; VOLKOW, 2010). Por este motivo, muitos indivíduos com transtornos de humor e ansiedade são bastante propensos ao consumo elevado de etanol com o intuito de aliviar os sintomas psiquiátricos (BECKER; LOPEZ; DOREMUS-FITZWATER, 2011).

Os transtornos de humor e ansiedade vêm recebendo bastante atenção nos últimos anos, visto que cada vez mais pessoas manifestam essas doenças graças ao estresse da vida moderna e a outros traumas. Muitos pacientes não os compreendem como doenças, de forma que poucos procuram tratamento especializado e acabam consumindo drogas de abuso como forma de automedicação (BACK; BRADY, 2008). De fato, dados de diversos estudos mostram que existe uma correlação entre o abuso e dependência de álcool e outras drogas com transtornos psiquiátricos. O II Levantamento Nacional de Álcool e Drogas (II LENAD) mostra que 40,9% da população com problema de álcool apresentam indicadores de depressão (LARANJEIRAS et al., 2012). Além disso, estudos de meta-análise de pesquisas epidemiológicas afirmam que aproximadamente 35% dos indivíduos com transtorno de uso de álcool portavam algum transtorno de humor e, entre estes, mais de 50% apresentavam algum tipo de transtorno de ansiedade, dentre os quais se destacam o transtorno de estresse pós-traumático, o transtorno de pânico, a fobia social e o transtorno de ansiedade generalizada (LAI et al., 2015; GIMENO et al., 2017). A automedicação alivia os sintomas de estresse e ansiedade presentes nessas síndromes, entretanto, o consumo crônico de etanol e o desenvolvimento de dependência estão associados ao aumento nos níveis de estresse e, dessa forma, pode agravar os sintomas desses transtornos psiquiátricos.

Estudos recentes indicam a importância do ambiente para o desenvolvimento de transtornos psiquiátricos, incluindo o transtorno de uso de substâncias (NITHIANANTHARAJAH; HANNAN, 2006; SOLINAS et al., 2010). O enriquecimento ambiental (EA) expõe os animais de laboratório à maior estimulação física, devido às rodas de exercícios; sensorial, pelo contato com objetos diferentes aos do alojamento padrão; e também o aumento de interações sociais com outros animais (NITHIANANTHARAJAH; HANNAN, 2006). Pouco se sabe como o EA produz efeito protetor contra a adicção, porém acredita-se que um dos mecanismos seja pela regulação dos sistemas de estresse (SOLINAS et al., 2010).

A oxitocina (OT), por sua vez, é um hormônio liberado em resposta a interações sociais e fortemente associado às emoções positivas (NEUMANN, 2008). Defende-se que a OT atue sobre os sistemas encefálicos que regulam a resposta de estresse, reduzindo os sintomas emocionais negativos (NEUMANN; SLATTERY, 2016). O sistema de estresse possui atividade aumentada em vários transtornos psicossociais, incluindo os transtornos de ansiedade e o alcoolismo (KOOB, 2008). Dessa forma, espera-se que a OT possa ser utilizada como tratamento para essas doenças ou pelo menos para o alívio dos sintomas. Além disso, acredita-se que a OT seja capaz de modificar a sinalização do centro dopaminérgico mesolímbico de recompensa, conferindo resiliência ao estresse e assim, efeito protetor contra a adicção (KOVÁCS; SARNYAI; SZABÓ, 1998).

Como o EA aumenta as interações sociais e altera o *binding* a receptores de OT (OTR) (RAE et al., 2018), nosso laboratório investiga o papel deste hormônio no EA como agente endógeno no tratamento da dependência de álcool. Dessa forma, espera-se que o trabalho colabore com os conhecimentos atuais sobre a importância do ambiente e de uma boa qualidade de vida para a redução do consumo de etanol. Assim, além de fornecer benefícios individuais, como a recuperação da saúde do indivíduo, o menor consumo de álcool pode proporcionar melhorias à sociedade, diminuindo os acidentes de trânsito, os níveis de desemprego, além de todos os custos envolvidos no sistema criminal, em hospitais e outras instituições responsáveis pelo tratamento desses indivíduos.

## 6 CONCLUSÃO

O transtorno de uso de substâncias ainda é bastante estigmatizado pela população. Contudo, é necessário compreender que a dependência é uma doença que ocorre após uma série de alterações no sistema nervoso central que impede que o indivíduo consiga controlar o próprio consumo. As modificações são tão intensas que, mesmo que o dependente esteja em abstinência por um longo período de tempo, uma situação de estresse pode induzi-lo à recaída. Poucos são os fármacos disponíveis para o tratamento, uma vez que o transtorno tenha se instalado. Dessa forma, a pesquisa em dependência de drogas tenta entender os fatores fisiológicos subjacentes para desenvolver tratamentos cada vez mais eficazes.

O ambiente influencia fortemente o fenótipo de dependência. Indivíduos que vivem em condições inóspitas são mais vulneráveis aos efeitos das drogas de abuso, por isso apresentam maior probabilidade de adquirir o transtorno. Por outro lado, condições ambientais positivas oferecem proteção ao desenvolvimento da dependência. Neste trabalho, foi demonstrado que o enriquecimento ambiental é capaz de reverter o aumento do consumo de etanol em camundongos com histórico de dependência, após serem expostos a um estresse por exposição ao rato, que é utilizado como modelo de TEPT.

Devido ao fato do EA induzir estímulos sociais, entende-se que o sistema oxitocinérgico deve atuar como um dos componentes endógenos de sua ação. De fato, nosso laboratório mostrou que o perfil de distribuição dos receptores de OT se altera com o EA (RAE et al., 2018). Por isso, postulamos uma hipótese de que o consumo de etanol diminuiria com a ativação repetida dos receptores de oxitocina, caso ela ocorresse durante o mesmo período de tempo que o EA passa a ter os seus efeitos protetores. Contudo, descobrimos que a estimulação oxitocinérgica por meio de agonistas exógenos pode bloquear o escalonamento de etanol induzido pelo estresse, mas também é bastante dependente do horário do tratamento.

A maioria dos estudos mostrando os efeitos ansiolíticos e protetores da oxitocina contra o consumo de drogas foi realizado utilizando doses agudas, enquanto os poucos que fizeram um tratamento crônico mostram resultados pouco promissores para iniciar o uso da OT como medicamento ansiolítico. Apesar de muitos destes trabalhos mostrarem

resultados divergentes, ora com efeitos ansiolíticos, ora com efeitos ansiogênicos, todos eles afirmam a importância do contexto para a resposta obtida. Neste trabalho, mostramos que a CBT tem efeitos positivos sobre o consumo de etanol em animais abstinentes, porém seus efeitos após estresse dependem do momento que o fármaco é administrado. Dessa forma, ainda são necessários mais estudos para avaliar a possibilidade de utilizar a OT como tratamento para o consumo abusivo de álcool, já que, dependendo do contexto, ela pode inclusive gerar efeitos deletérios.

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