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RESEARCH HIGHLIGHT

A role for α7 nicotinic receptors in promoting stress resilience in female mice

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Despite the higher prevalence of depression in women than men, most studies involving animal models of depression have used only male subjects [1]. This clear disconnect between clinical and preclinical research has almost certainly hampered our understanding of the distinct neuronal mechanisms associated with depression in women, potentially limiting the development of novel therapeutic strategies aimed at ameliorating depression in this population. This gap in our knowledge highlights the critical importance of conducting preclinical studies in both male and female subjects to better understand common and divergent mechanisms of complex neurobiological disorders.

In this issue of *Neuropsychopharmacology*, Ortiz et al. [2] highlight the differences in neuronal mechanisms that contribute to susceptibility to depression in female subjects. To do this, they used a recently described model of chronic social defeat stress adapted to female mice, where female mice are treated with male odorants in order to elicit aggressive social encounters with males [3]. The authors reported several important observations. First, approximately half of the female mice experiencing stress after chronic social defeat interacted less frequently with other mice and showed a reduced preference for sucrose. The observation that not all mice showed these effects is consistent with the idea of "stress-susceptible" and "stress-resilient" phenotypes [3]. Next, the authors showed that the behavioral changes observed in the stress-susceptible mice are reversed by a single dose of ketamine, a dissociative anesthetic with antidepressant effects. Thirdly, using in vitro electrophysiology, the authors found that dopamine neurons in the ventral tegmental area (VTA) of susceptible, but not resilient mice displayed enhanced firing rates, and this stress-induced change was also reversed by ketamine. Next, since prior studies showed a role for cholinergic inputs in regulating dopamine neuronal activity, the authors used cell-specific retrograde labeling to examine the origin of these cholinergic inputs to the VTA and whether they are altered by chronic social defeat stress. They found that cholinergic neurons in the lateral dorsal tegmentum (LDTg) that project to VTA dopamine neurons displayed increased excitability in both resilient and susceptible mice, relative to naive controls; a finding consistent with previous work demonstrating an important role for this pathway in social defeat stress in males [4].

The authors then evaluated the effects of direct activation α7 nicotinic receptors (nAChRs) on VTA dopamine neurons by local application of nicotine and found that α7-mediated currents were smaller in VTA dopamine neurons from stress-resilient mice compared to naive and susceptible mice (Fig. 1). This suggests that social defeat stress leads to distinct adaptations in postsynaptic α7 function on these neurons to compensate for enhanced cholinergic input, thereby promoting stress resilience. This hypothesis was examined by using a positive allosteric modulator of α7 receptors known as PNU-120596 given before a mild, subthreshold, social defeat procedure. Neither naive nor vehicle-treated mice displayed reduced social interaction behavior after this mild stressor. However, mice treated with PNU-120596 displayed reduced social interactions, as well as increased VTA dopamine neuron excitability after the subthreshold social defeat procedure. Reduced social interactions were also observed when PNU-120596 was given 24 h following subthreshold defeat, suggesting a broad temporal window following mild stress during which α7 receptor activation can influence depressive-like behaviors. Lastly, and perhaps most remarkably, the authors showed that PNU-120596 treatment led previously resilient females to display increased stress susceptibility, suggesting a strong causal link between α7 receptor efficacy and depression-like symptoms in female mice.

Together, these results provide compelling evidence that LDTg cholinergic inputs to VTA DA neurons influence the stress-induced depressive phenotype in female mice through α7 nAChRs, as was previously demonstrated in males.

The study by Ortiz et al. [2] emphasizes the importance of translational studies designed to compare males and females. Although the model developed by Harris et al. [3] used in this study may be somewhat artificial in nature (e.g., promoting social defeat in females by pretreating them with male odorants), it nevertheless represents a useful model of depression in females. Importantly, the fact that Ortiz et al. showed that ketamine reversed both behavioral and electrophysiological changes in this model suggests that it may have predictive validity. In addition, the electrophysiological changes in VTA dopamine neuron activity, as well as the contributions of α7 nAChRs reported in this study are consistent with previous studies in male mice after chronic social defeat, suggesting that common substrates underlie some depressive behaviors regardless of sex. The upregulation of cholinergic activity, together with the ability of α7 nicotinic receptors on VTA dopamine neurons to influence the susceptibility to stress, may have important therapeutic implications. Indeed, the close association between nicotinic receptors and

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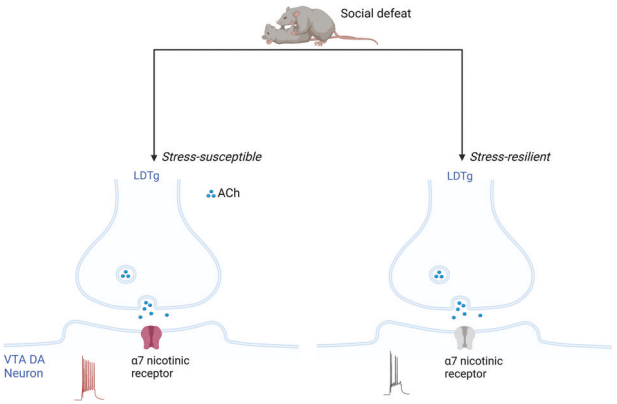

Fig. 1 Chronic social defeat stress in female mice leads to enhanced cholinergic (ACh) signaling from the LDTg→VTA. In stress-susceptible mice, VTA neurons display normal α7 nicotinic receptor function and increased activity. However, resilient mice display smaller α7-mediated currents and reduced DA neuronal activity. Figure created in Biorender.com.

mood disorders [5] suggests that these findings should be of general interest to those examining interactions between smoking and depression, anxiety, or other psychiatric conditions. Given the role of VTA dopamine neurons in regulating motivational states through their connections to both subcortical and cortical nuclei, it will be important to further determine the contributions of other brain regions to regulating stress resilience or susceptibility. Since ketamine and PNU-120596 act at multiple sites throughout the CNS, future studies should address the role of specific circuits by using local drug infusions rather than systemic injections. Nevertheless, by highlighting the importance of cholinergic regulation of VTA function in this novel animal model, this study makes an important, and long overdue, contribution to the evaluation of the potential neuronal mechanisms underlying depression in females.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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