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RESEARCH HIGHLIGHT

Adding dopamine to the complexity of sex differences in opioid reinforcement

Hannah L. Robinson[1] and Matthew L. Banks[1]✉

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The opioid crisis continues to be a serious public health problem despite the availability of several effective pharmacotherapies. The progression from opioid misuse to opioid use disorder (OUD) involves complex interactions between the subject, the environment, and the opioid. One subject-related variable that has consistently been shown to influence OUD is sex. For example, despite higher prevalence of prescription opioid use in females compared to males, the rate of prescription opioid misuse, prescription OUD, and past year heroin use are all approximately twice as high in males [1, 2]. In contrast, females were reported to transition faster than males to OUD as defined as the time from first drug use to methadone maintenance admission [3, 4]. These complex interactions between the subject, the environment, and the abused opioid have also be reported in preclinical studies [5]. In summary, these clinical and preclinical data highlight the complexity of sex as a biological variable in the expression and potential mechanisms of OUD and support preclinical research efforts to disentangle these interactions.

In this issue of *Neuropsychopharmacology*, George et al. evaluated sex differences in acquisition, potency, heroin-seeking behavior, and escalation of heroin self-administration in female and male rats [6]. The authors then paired these behavioral measures with assessment of dopamine release in the nucleus accumbens shell using fast-scan cyclic voltammetry and mu-opioid receptor expression in the ventral tegmental area and nucleus accumbens. There were five main findings. First, there were no sex differences in acquisition of heroin self-administration. Second, the heroin dose-response self-administration function was shifted upward in females compared to males without an apparent sex difference in the reinforcing potency of heroin (i.e., female rats responded at higher rates for opioid injections than males). In addition, females exhibited higher rates of responding for heroin-associated discriminative stimuli compared to males. Third, females displayed greater escalation of heroin self-administration than males under daily long-access sessions (6 h/day). Fourth, there was no effect of heroin or sex on mu-opioid expression in ventral tegmental area and nucleus accumbens under the long access conditions. Lastly, a history of long access heroin self-administration resulted in a similar increase in dopamine transporter activity in both sexes. However, nucleus accumbens shell dopamine release was selectively enhanced in females with a heroin self-administration history compared to heroin-naïve controls, an effect that was not observed in males. The behavioral sex differences are consistent with the hypothesis that females display higher rates of opioid-maintained operant behavior than males and might suggest "vulnerability" to opioid misuse. However, we note that these data are seemingly inconsistent with the human literature, which suggest women are not more vulnerable than men to opioid craving and relapse (for recent review, see preprint [6]).

Regarding the voltammetry results, the role of dopamine in opioid self-administration has been a debated subject in the drug abuse field. However, recent evidence using optogenetic techniques has provided evidence for both mesolimbic and nigrostriatal pathways in opioid reinforcement and reward (for a recent review, see [7]). One caveat of these recent studies using optogenetic techniques is that these studies generally used relatively short self-administration sessions (~1–2 h), which are unlikely to be sufficient to establish opioid dependence or elicit somatic withdrawal signs upon opioid abstinence. This may be an important consideration, as opioid withdrawal has been emphasized by OUD patients as a primary factor for continued opioid use and relapse [8]. The results of George and colleagues provide evidence for the role of dopamine in opioid self-administration following a potentially opioid-dependence inducing history of heroin self-administration (6-h sessions), although the expression of somatic withdrawal signs was not assessed. Understanding how dopamine transporter function and neurotransmission is impacted by the degree of opioid dependence and withdrawal will be an important future direction to improve our mechanistic understanding of sex differences in opioid reinforcement and may aid in the development of personalized OUD medications.

The findings reported by George et al. raise a number of intriguing research directions to improve our understanding of how sex as a biological variable mechanistically impacts opioid self-administration. For example, the authors propose there may be sex-dependent differences in the consequences of long-access heroin self-administration on mu-opioid receptor function or signaling on GABAergic ventral tegmental area neurons. This hypothesis suggests that repeated opioid self-administration leads to sex-specific neuroadaptations, which could promote behavioral sex differences undetectable under short-access conditions. Notably, this hypothesis is consistent with our recent report of behavioral and transcriptomic sex differences in rats undergoing spontaneous withdrawal from a regimen of long-access (12 h) fentanyl self-administration [9]. Ultimately, improved understanding of these complex interactions between the subject, environment, and the opioid drug will lead to the development of safer

[1]Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, USA. ✉email: mbanks7@vcu.edu

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and more effective therapeutic strategies towards a personalized medicine approach [10], including sex as a biological variable.

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AUTHOR CONTRIBUTIONS

HLR and MLB contributed equally to conceptualization, drafting, editing, and finalizing the manuscript. HLR and MLB approved the final manuscript version for publication.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to M.L.B.