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RESEARCH HIGHLIGHT

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A dubious distinction for females: rapid achievement of prefrontal cortical hypoactivity and cognitive deficit upon remifentanil self-administration

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Humans have long ingested opioids. In 1797, an opium-induced dream inspired Samuel Taylor Coleridge's famous poem "Kubla Khan". 100 years later, Arthur Conan Doyle's Sherlock Holmes and Dr. Watson meet unexpectedly in an opium den in "The Man with the Twisted Lip" (1891), where Sherlock accuses Watson of assuming the worst (but Sherlock was searching for information, not opium). Recently, opioid misuse has escalated, resulting in what we now refer to as the "opioid overdose crisis," a period of time characterized by rates of overdose-induced deaths unprecedented in modern history.

Opioid use disorders afflict males and females, but females are more likely to use prescription opioids, and opioid-related death are increasing more rapidly among females [1]. Neuroimaging studies document *hyper*activity of medial prefrontal cortical regions in response to heroin-related cues in heroin-addicted individuals, and *hypo*activity in basal states (discussed in ref. [2]). Similar phenomena are reported in (mostly male) rodents self-administering cocaine (discussed in ref. [2]). In this issue, a new, comprehensive report by Anderson et al. [2] dives deeply into the neurobiological consequences of opioid self-administration on prefrontal cortical physiology and function, investigating effects across time and sexes.

The investigators trained male and female mice to self-administer remifentanil, an opioid used clinically to treat pain. Mice self-administered for 10–16 days, which I will refer to as "moderate exposure," or 25–30 days, referred to as "extended exposure." Following self-administration, the mice received a 14–21-day or longer washout period. Control mice received saline infusions paired with Ensure to promote the acquisition of operant responding and control for effects of motor activity.

In initial experiments using moderate remifentanil exposure, females developed basal hypoactivity of layer 5/6 pyramidal neurons in the prelimbic prefrontal cortex (PL). Meanwhile, males exhibited hyperactivity despite similar patterns of drug intake. With extended exposure, both males and females developed hypoactivity. Thus, remifentanil self-administration decreases the basal activity of PL neurons. This effect develops more rapidly in females and is unexpectedly preceded by a period of *hyper*activity in males.

The investigators next measured patterned spike firing, revealing increased firing with more depolarized potentials following moderate remifentanil exposure in females. This pattern again developed *only with extended exposure* in males. And interestingly, basal hypoexcitability and modestly elevated firing capacity were evident in females even following a prolonged washout period. Thus, remifentanil-induced hypoactivity and elevated firing capacity of PL neurons develop more rapidly and are more persistent in female mice.

The authors then reveal through pharmacological manipulations that hypoactive basal states in females are associated with decreased AMPA-mediated excitatory drive. Meanwhile, hyperactive and hypoactive states in males are instead associated with $GABA_B$ signaling. If one were to attempt to treat opioid misuse using novel disease-modifying strategies, these findings are rather impactful—suggesting that treatments in males and females should fundamentally differ.

The authors also tested the capacity of remifentanil self-administering mice to perform an attentional set-shifting task, conceptually similar to the Wisconsin Card Sort task in humans. In striking parallel with physiological patterns, females struggled to perform extradimensional shifts (task phases with the greatest complexity) and generated errors after only moderate remifentanil exposure. Meanwhile, males required extended exposure to develop the same deficits.

Finally, the authors turned to Gq-coupled designer receptors exclusively activated by designer drugs (DREADDs). Gq-DREADD stimulation in the PL restored performance in the attentional set-shifting task following remifentanil, implicating opioid-induced PL hypoactivity in poor cognitive function. Anderson et al. thus clearly connect drug-induced neuromodulations with cognitive deficits, and in particular cognitive deficits associated with the PL.

Another key function of the PL is linking actions and outcomes, a process necessary for goal-directed behavior—selecting actions likely to be rewarded with desirable outcomes [3]. Some argue that addictive drugs degrade this ability and cause organisms to favor habit-based behaviors, which are stimulus-elicited and insensitive to outcomes. Notwithstanding debates regarding whether habitual behavior directly contributes to addiction, it

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Fig. 1 A dubious distinction for females. Anderson et al. [2] reveal that female mice self-administering remifentanil develop hypoactivity of layer 5/6 neurons in the PL, coupled with impairments in an attentional set-shifting task, more rapidly than self-administering males. Illustration courtesy of Aylet Allen.

would be interesting to determine whether opioid-induced hypoactivity of PL neurons degrades the capacity for goal-oriented action. Female mice defer to habitual behavior following lower doses of cocaine than males and display considerable individual differences [4], raising the possibility that females could have similar vulnerabilities/variabilities in the context of opioid exposure as well.

Anderson et al. speculate that PL neurons expressing dopamine D1 receptors (D1R) are involved in the physiological and behavioral effects of opioid exposure (see also their related report, ref. [5]). These cells project to both D1R+ and D2R+ medium spiny neurons in the posterior dorsomedial striatum (pDMS) [6]. This pattern is significant because in the pDMS, D1R + neurons are necessary for response strategy shifting when response-reward contingencies change—for instance, when a familiar lever press fails to be reinforced and rats must shift to another lever to gain reward [7]. This D1R + PL-to-pDMS pathway could be a focus of future investigations concerning the neurobiological consequences of opioid exposure.

A constellation of proteins in the PL is necessary for optimal goal seeking (summarized in ref. [3]). Meanwhile, *suppressing* other proteins like Rho-kinase and PI3-kinase p110β in the PL can decrease cocaine-induced habitual behavior [8, 9]; whether they are impacted by opioids and/or withdrawal could also be investigated.

A final note concerns Anderson et al.'s focus on layer 5/6 neurons in the PL. These neurons are particularly attuned to the response and outcome phases of attentional set shifting tasks, particularly *following* these task epochs, suggesting that they receive inputs providing feedback to crystalize response strategies, rather than providing top-down control over behavior [10]. Whether remifentanil-exposed PL neurons lose the ability to integrate inputs from regions like the anterior cingulate could be investigated.

The opioid crisis is a pervasive issue, yet much of what we believe regarding the long-term neurobiological consequences of drug self-administration stems from studies of cocaine exposure in (male) rodents. Anderson et al.'s enormous effort sheds fresh light onto long-term ramifications of a clinically-used opioid within the prefrontal cortex, and in both sexes. In this case, females appear to have the dubious honor of "winning the race," developing remifentanil-induced hypoactivity within the PL and cognitive disruption more rapidly than males (Fig. 1).

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COMPETING INTERESTS

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