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RESEARCH HIGHLIGHT

The lasting impact of methocinnamox on opioid self-administration

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Although a decline in fatal opioid overdoses was observed in the United States in 2018, the number of these deaths remained alarmingly high (46,802 fatalities) [1]. Addressing this worldwide opioid crisis will require basic science research to develop and evaluate improved treatment strategies for opioid-use disorder (OUD). Currently, three pharmacotherapies for OUD are available as follows: the high-efficacy μ-opioid receptor (MOR) agonist methadone, the low-efficacy MOR agonist buprenorphine, and the competitive MOR antagonist naltrexone. Methadone and buprenorphine are among the World Health Organization's *List of Essential Medicines* [2], but their clinical utility is constrained by abuse-liability concerns. Naltrexone does not possess the abuse-liability concerns of methadone and buprenorphine, and has fewer restrictions outside of the requirement that patients be non-opioid dependent. However, the effectiveness of naltrexone is often unrealized due to poor patient compliance and the potential of surmountability of its competitive antagonism by increased MOR agonist consumption [3].

In the current issue of *Neuropsychopharmacology*, Maguire et al. [4] determined the effectiveness of acute and repeated methocinnamox (MCAM) treatment to attenuate fentanyl self-administration in male and female rhesus monkeys. Previous works of the authors have reported acute MCAM treatment to prevent and reverse the respiratory-depressant effects of heroin [5] and decrease the choice of remifentanil over a food alternative [6]. MCAM is a putative pseudoirreversible MOR antagonist, meaning that it binds non-competitively to MORs, albeit non-covalently. Therefore, receptor turnover is hypothesized to be a primary limiting factor to its duration of action [4]. The pharmacokinetic and behavioral results supported this hypothesis, as the plasma half-life of a single MCAM dose (~70 min) was much shorter than its duration to reduce fentanyl self-administration (13 days). In contrast, an equi-effective naltrexone dose decreased fentanyl self-administration for only 1 day. Repeated MCAM administration (five doses across a 48-day period) produced sustained decreases in fentanyl self-administration without altering cocaine self-administration, demonstrating behavioral selectivity. Furthermore, fentanyl self-administration did not recover until 24 days after the final MCAM injection. This long and sustained duration of action by MCAM would potentially prolong clinical dosing intervals and mitigate some of the patient compliance issues associated with once-monthly depot naltrexone formulations [3].

An additional and exciting prospect for the clinical utility of MCAM is insurmountable antagonism of MOR agonist effects. Figure 1 uses simulated data and concepts of Receptor Theory (see ref. [7]) to illustrate the fundamental differences between competitive and non-competitive (irreversible) antagonism of an agonist dose–response function. In the absence of an antagonist, increasing doses of an agonist progressively activate receptors (solid line). Different agonist effects (e.g., reinforcement vs. respiratory depression) require different levels of receptor activation. For example, if we arbitrarily designate the receptor activation "window" for fatal respiratory depression between 60% and 75% (rectangle "A"), and the receptor activation window for reinforcement between 25% and 40% (rectangle "B"), this example would suggest a lower level of MOR activation is required to produce abuse-related vs. respiratory-depressant effects. Competitive antagonists such as naltrexone compete with the agonist at receptors and produce parallel rightward shifts of the agonist dose–response function [7]. Figure 1 shows that a fivefold larger agonist dose surmounts the effects of the competitive antagonist (dashed line), achieving sufficient receptor activation for both reinforcing and respiratory-depressant effects. Conversely, pseudoirreversible antagonists like MCAM non-competitively bind to receptors,

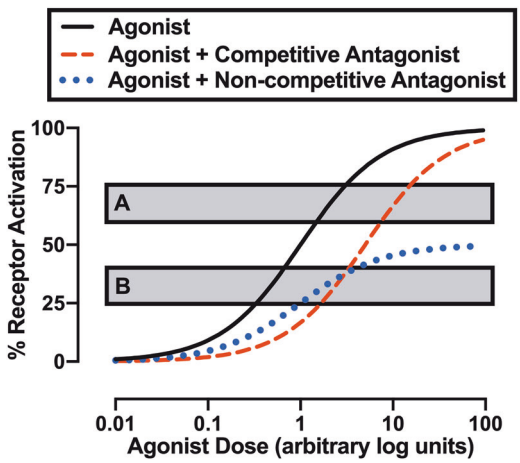

Fig. 1 Use of simulated data to compare the effects of competitive (dashed line) and non-competitive (dotted line) antagonism on an agonist dose–response function (solid line). Ordinate: percent receptor activation. Abscissa: agonist dose. Curves simulated using the Furchgott equation of Receptor Theory as reported in ref. [7].

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which reduce the number of receptors available to the agonist and produce downward shifts of the agonist dose–response function [7]. The magnitude of an irreversible antagonist effect depends on (1) the number of receptors occupied by the antagonist, (2) the efficacy requirement of the MOR agonist effect (i.e., position of the "window"), and (3) the intrinsic efficacy of the MOR agonist (i.e., magnitude of irreversible antagonist effect decreases with increasing agonist efficacy [8]). Figure 1 shows the predicted effects on an agonist dose–response function if a non-competitive antagonist (e.g., MCAM) is administered at a dose that decreases the efficacy of the agonist by half. Here, non-competitive antagonist effects within the "reinforcement window" (rectangle "B") would be surmountable, whereas non-competitive antagonist effects within the "respiratory depression window" (rectangle "A") would be insurmountable. Thus, a promising clinical implication is that MCAM could eliminate the ability of MOR agonists to produce overdose, given that MCAM could be delivered in sufficient quantities.

Overall, the findings of Maguire et al. [4] contribute to a growing body of compelling evidence (e.g., see refs. [5, 6]), warranting the further consideration of MCAM as a candidate medication for OUD and/or opioid overdose. The translational potential of these results were enhanced by (1) repeated MCAM treatment effects, (2) measures of behavioral selectivity (fentanyl vs. cocaine self-administration), (3) a positive control comparator (naltrexone), and (4) non-human primates as subjects (see ref. [9]). However, whether MCAM-mediated antagonism of reinforcing or respiratory-depressant effects are insurmountable remains to be empirically determined.

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ADDITIONAL INFORMATION

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