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Commentary

COMMENTARY

Molecular-container Calabadion-2: Can Sweeping the Brain of Drugs Promote Abstinence?

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The abuse of psychostimulant drugs has been a serious public health concern for a long time, yet there are no effective treatments for stimulant use disorder (SUD). Methamphetamine (METH) is one of the most commonly abused psychostimulant drugs because of its strong addictive potential, evidenced by high rates of drug relapse in abstinent METH users, as well as its wide illicit availability. Preclinical studies that model drug relapse have identified mechanisms underlying drug relapse and craving, which can be triggered by acute reexposure to the self-administered drug (De Wit, 1996), drug-associated cues (O'Brien et al., 1992), or stressors (Sinha, 2011). Current treatments for relapse in abstinent METH users primarily involve cognitive and behavioral therapies, which have limited efficacy (Lee and Rawson, 2008). No effective pharmacological treatments for relapse prevention in abstinent METH users have been developed. Most studies working to identify pharmacological approaches to reduce drug relapse (reinstatement in animals) have focused on dopamine neurons in the ventral tegmental area (Shalev et al., 2002; Schmidt et al., 2005) and associated circuitry involving glutamate, norepinephrine, opioids, and corticotropin releasing factor (CRF) neurons (for review, see Mantsch et al., 2016), which are all known to affect critical circuitry underlying reinstatement of drug seeking in animals. Pharmacological modulation of dopamine systems with dopamine antagonists to reduce the reinforcing effects of METH, the use of direct or indirect dopamine agonists as a type of replacement therapy, and the use of drugs that might indirectly modulate dopaminergic activity, such as naltrexone, have all been investigated (for review, see Brensilver et al. 2013) but have not resulted in the development of a successful clinical treatment. A very different conceptual approach to SUD treatment is a pharmacokinetic approach that involves the removal of the drug from the bloodstream before it can affect brain function. This approach has used antibodies targeting particular drugs of abuse, including METH, with the aim of reducing the free plasma concentration of the drug to minimize its effects (Gorelick, 2012). Such approaches reduce some behavioral effects of METH (and other drugs of abuse), but variations in antibody titers and other factors have resulted in inconsistent outcomes in preclinical as well as clinical trials. Since the primary shortcomings of these studies are technical, the underlying principal may still prove effective if these can be overcome, either through innovations in the antibody approach or through an alternative pharmacological approach.

The calabadion family of acyclic cucurbit[n]uril "molecular containers" binds drugs and facilitates their removal from the circulation and the body and were developed for the purpose of quickly terminating the actions of neuromuscular-blocking agents (Hoffmann et al., 2013). An initial survey of these molecules found that calabadion-2 (Cal-2) has a high affinity for (+)-methamphetamine in vitro (Ganapati et al., 2017) and that administration of Cal-2 reduces the locomotor stimulant effects of METH in vivo, seeming to confirm the potential mechanism of action of the drug. To further evaluate the potential of Cal-2 to reduce METH effects that may be relevant to relapse prevention, Leonard et al., in this volume, investigated the effects of Cal-2 on METH reinstatement as a model of relapse. The effects of Cal-2 on the reinstatement of METH seeking were examined after a period of forced abstinence in response to METH and yohimbine. Yohimbine-induced reinstatement has often been thought to result from a stress-like activation of norepinephrine neurotransmission, although other effects of yohimbine may underlie these effects (Chen et al., 2015). In the present study, yohimbine may be considered to be a pharmacological control for the effects of Cal-2 on METH or as a comparison between drug-induced and stress-induced reinstatement. Cal-2 reduced METH-induced reinstatement, presumably by increasing

the elimination of METH, but it had no effect on yohimbine-induced reinstatement. The yohimbine results further indicate the mechanism of action of Cal-2 does not directly affect neural mechanisms underlying reinstatement and thus contributes to our understanding of the results. The effects of Cal-2 on METH-induced reinstatement support the idea that Cal-2 might be a potentially effective treatment for drug relapse in METH users, although it should be noted that the authors indicated that the effect of Cal-2 could be overcome with a higher METH dose; those data, however, were not fully presented. In any case, given the potential ability of a higher METH dose to overcome the effect of Cal-2 on METH-induced reinstatement, it would be interesting to examine the effects of Cal-2 on ongoing METH self-administration. In particular, it would be important to determine whether Cal-2 would produce reductions in METH self-administration or compensatory increases in drug-taking. This would have potentially important implications for Cal-2, or similar drugs, to effectively treat SUD.

The absence of an effect on yohimbine-induced reinstatement suggests that Cal-2 may not address other important causes of reinstatement such as those associated with stimulus-induced craving and stress-induced drug seeking. Based on the mechanism thought to underlie the present effects, the reduction of METH effects should result from its elimination from the blood and the body, preventing it from acting in the brain. If this is the case, Cal-2 would not be predicted to prevent conditioned stimulus-induced or stress-induced reinstatement. These limitations could prove problematic clinically if stress or responses to conditioned stimuli are more common factors influencing relapse, which is likely given that craving and drug seeking would presumably precede drug consumption after a period of abstinence in most patients. These are potential limitations of the principal being addressed here, although, all the same, it is likely that the approach could have clinically significant effects on relapse prevention and abstinence promotion.

Providing that such an approach does have clinically significant effects for SUD, there are still issues with Cal-2 itself as a potential medication, as recognized by the authors of this article, although it may nonetheless be a good starting point for drug development. Several drugs that act in a similar manner to Cal-2 are used clinically to counteract the effects of neuromuscular-blocking agents, and Cal-2 has been investigated for this use (Hoffmann et al., 2013). These drugs are used intravenously, which is an effective mode of administration given the clinical goals for which they are used, a quick reversal of drug actions. However, an i.v. treatment would be less useful in the treatment of a chronic, relapsing disease such as SUD. Of additional importance for this type of treatment approach, Cal-2 also has a short half-life, which might limit its effectiveness for the treatment of SUD. An additional consideration for the circumstances in which such a drug would be used to treat SUD is compliance, which is likely to be problematic in the treatment of SUD.

Although this paper primarily considered the effect of this drug mechanism on relapse to drug taking, the principle underlying this therapeutic approach should also be considered in the context of drug overdose. The potential for eliminating high doses of a toxic drug under circumstances of overdose would be exceptionally important. This is not just a consideration for opioids given the current opioid overdose epidemic but also continues to be important for other abused drugs, such as psychostimulants. This will be a critical need in coming years as the current drug overdose epidemic evolves and changes, including the apparent increase in the use of psychostimulant drugs in recent years (Hall and Miczek, 2019). It is worth noting that although Cal-2 was unable to overcome the effects of a 10-fold higher dose of METH on METH-induced reinstatement (data not presented), so it will be important to examine the potential for higher Cal-2 doses to treat high-dose METH effects such as occur in an overdose situation.

Although Leonard et al. suggested that Cal-2 acts on METH reinstatement by binding METH in the circulatory system and increases METH elimination, this remains to be directly demonstrated. In the same respect, it will be important to examine the specificity of Cal-2 for METH at this mechanistic level as well as at a phenomenological level, since stimulant abusers may use other METH analogues, sometimes in response to availability or price in the illicit market. Many other amphetamines and amphetamine-like compounds are also abused, so the potential of Cal-2 to limit the effects of other drugs of abuse would be of exceptional interest.

The findings of this study support the possibility that Cal-2-induced reductions in METH actions might be effective in reducing some types of METH-induced relapse and are a very important step forward in the study of this approach to the treatment of SUD. There are limitations for Cal-2 itself as a potential medication for the treatment of drug relapse in SUD as well as potential limitations of the approach in principle. Nonetheless, the data do show a proof of concept for this approach in the development of pharmacological interventions for METH abuse, and Cal-2 and similar drugs are worthy of further investigation both preclinically and clinically. Moreover, there may be applications for Cal-2 worth investigating beyond the prevention of relapse following abstinence, such as overdose reversal or reducing drug intake during self-administration.

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Interest Statement

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