Investigating Methamphetamine Craving Using the Extinction-Reinstatement Model in the Rat

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Summary
Like all other drugs of abuse, the primary therapeutic objective for treating methamphetamine addiction is the maintenance of abstinence and prevention of relapse to habitual drug-taking. Compounds with the potential to prevent relapse are often investigated in rats that are trained to self-administer intravenous methamphetamine, subjected to extinction training where responding is no longer reinforced, and then given tests for reinstatement of drug-seeking behavior triggered by methamphetamine injections or re-exposure to drug-paired cues. Experimental compounds are administered to the animals prior to the reinstatement tests to evaluate their potential for preventing or reversing drug-seeking behavior. This article describes the common procedures of the extinction-reinstatement model in studies of this type, and identifies areas of discrepancy. This is followed by a comprehensive overview of the currently published anti-reinstatement effects of pharmacological compounds, classified by the most relevant neurological systems associated with these compounds. The article concludes with a brief discussion of how the study of anti-reinstatement effects can be expanded to further verify existing positive results or to find novel neurobiological targets.

Introduction
Compulsive abuse of and addiction to methamphetamine, a psychostimulant with reinforcing properties resembling those of cocaine, is a significant and rapidly growing global health problem [1]. After marijuana, methamphetamine is the most abused illicit drug in the world [2]. Currently no medications have been approved by the Federal Drug Administration for the treatment of addiction to psychostimulants, including methamphetamine. The conceptualization of addiction has been evolving towards that of a chronic disease, and consequently research efforts have focused on developing treatments to reduce the likelihood of relapse in abstinent individuals [3]. Relapse is preceded by drug craving, which is commonly brought about not only by re-exposure to the drug, but to environmental stimuli previously associated with past drug use [4]. In order to facilitate the development of anti-relapse treatments, preclinical models have been developed that represent craving as the reinstatement of previously methamphetamine-reinforced activity provoked by non-contingent drug exposure or cues conditioned to drug reward [5,6]. Studies using rats with a history of methamphetamine self-administration have been utilized to test the therapeutic potential of a range of compounds that span a wide variety of neurobiological systems [7].

The most popular and powerful procedure available to study drug craving in small animals is the extinction-reinstatement model. Typically used in rats, this model comprises of initial training where the subject acquires stable self-administration of the drug, followed by a period of extinction training and test sessions utilizing presentation of environmental stimuli previously associated with drug reinforcement [8]. Whether this technique provides a valid approximation of human craving and relapse to drug seeking is a topic of active debate [9-11]. This review is an overview of the use of conditioned reinstatement experiments to evaluate the therapeutic potential of various compounds toward the relief of methamphetamine addiction. Commentary is provided regarding the extent to which each of the major neurobiological systems has been investigated.

Common Training and Testing Procedures
Although several variants of the extinction-reinstatement model have been developed for the study of cocaine and heroin seeking [12], the so-called between-session procedure [13,14] has been almost universally applied in recent experiments targeting methamphetamine reinstatement (Figure 1). The stages of training and testing described below mirror those of the majority of experiments testing for effects on cocaine reinstatement, and hence inherit their strengths and shortcomings.

Self-administration training
To condition rats to the reinforcing effects of methamphetamine, they are first trained to self-administer the drug by pressing a lever or exerting a nosepoke in the presence of response-contingent cues (usually a light or tone, or combination of the two). Methamphetamine is delivered via a surgically implanted intravenous catheter as reinforcement, using a dose usually ranging between 0.05 mg/kg and 0.1 mg/kg per infusion (Figure 2A). Training continues until a stable level of reinforced behavior is established, with a final reinforcement schedule ranging from FR 1 (where every active lever press is reinforced by methamphetamine, followed by a timeout period) to FR 5 (where reinforcement follows every five active lever presses). This period typically lasts from 10 to 16 days, using sessions of one to two hours in length.

The length of the self-administration experience in number of days, and in the number of hours per day, can have a profound effect on the physiology and behavior of rats exposed to many drugs of abuse, including methamphetamine [15,16]. When given longer access (six hr per session) to methamphetamine reinforcement, rats have been shown to gradually but significantly escalate their daily intake [17]. This increased intake of methamphetamine is a cardinal feature of the...
transition from drug abuse to addiction [18], and precipitates cognitive deficits as measured by novel object recognition and attention set-shifting [19,20]. Human chronic methamphetamine abusers are also known to significantly increase regular drug-taking following past experiences of unrestricted access [21], and demonstrate a variety of attention and cognitive impairments [22,23]. Exposing rodents to periods of extended drug access and/or intoxication has been termed the escalation model and has been developed in numerous studies of cocaine [24,25], morphine [26], heroin [27-29] and alcohol [30,31], all of which describe sustained enhancement in drug intake and evidence of dysregulated cognitive or stress-mediating systems that parallel clinical observations of drug and alcohol addicts [32]. The escalation model may therefore be a useful extension of the common short-access methamphetamine self-administration technique in preparing rats for the testing of potential therapeutic compounds [33,34].

**Extinction training**

All reinstatement experiments reviewed in this article describe a period of extinction training that follows self-administration, in which the rats are placed into the same operant chambers with the levers or nosepoke orifices available, but responses are not reinforced with drug delivery (Figure 2B). However, the conditions of extinction training beyond this definition vary considerably among studies. Methamphetamine infusions are either replaced by saline infusions [35] or no intravenous delivery of any kind [36]. Generally cues are not presented during extinction, but notable exceptions exist, where cues are presented during extinction training but not used for reinstatement testing [37,38] or are substituted with a set of inverse cue conditions signaling drug non-availability [39]. Most of all, variation exists in the conditions used for the termination of extinction training. In cases where a set number of extinction sessions are used, regardless of operant responding levels, this ranges from two days of 5-hr sessions [40] to 14 days of sessions using saline infusions [41]. Other studies used a criterion for operant responding to be achieved before terminating extinction training, usually a percentage (up to 20%) of the responses recorded at the end of self-administration training [36,39], or a set number of active lever presses per session [42,43]. These differences likely result in the length of the extinction period varying significantly among experiments, suggesting that rats in these studies were tested at different points of progress along what is properly considered a time-dependent learning process [44,45].

**Reinstatement testing**

After completion of extinction training, rats are tested for the reinstatement of methamphetamine-seeking behavior after administration of a pharmaceutical compound (Figure 2C). Reinstatement can be reliably induced by exposure to cues previously associated with drug reinforcement or non-contingent administration of the drug. In the studies reviewed here, these two triggers are most often used in separate experiments testing the same compound, with one exception where cues were used in combination with drug-priming injections [35]. This practice is a consequence of an accumulation of evidence that cue-elicited and drug-primed reinstatement behaviors are governed by distinct, yet overlapping, neurobiological substrates [46,12]. In fact, this notion has been confirmed in reports of different dose-response profiles for cue- and drug-elicited methamphetamine reinstatement [47,39]. These differences have been recently substantiated in the escalation model, where drug-induced but not cue-induced methamphetamine seeking was enhanced in rats with a history of prolonged exposure to drug availability [48].

In most of the studies reviewed here, the effects of pharmacologic compounds on reinstatement have been tested at various doses in a randomized within-subjects experimental design, ranging from two to six reinstatement tests with intervening periods of extinction retraining. This strategy provides an efficient and statistically potent assessment of the dose response of the anti-reinstatement effects, but is clearly vulnerable to the potential complicating factors of drug tolerance and behavioral fatigue. To our knowledge, the anti-reinstatement effect of a compound has been evaluated after chronic administration prior to the first reinstatement test in a small minority of studies [43,49,50]. This is an example of an acknowledged deficit in the field of drug seeking in animals, where potential therapeutic compounds are almost always tested once per subject per dose, despite the fact that clinical treatments are usually in the form of repeated treatments [51].

Besides non-contingent injections of methamphetamine and the exposure to drug-associated cues, stress-inducing experiences have also been found to result in reinstatement of methamphetamine-seeking behavior [37,52]. To our knowledge, exposure to intermittent footshock has only been utilized once to evaluate the anti-reinstatement effects of a compound in methamphetamine-trained rats [37], but this technique is known as the most reliable of stressful stimuli when inducing reinstatement of drug seeking [53,54]. However, since there is no human equivalent to footshock, the field of drug reinstatement has sought alternatives for inducing a more translatable stressful stimulus [55]. To date the most consistent stressor appears to be administration of yohimbine, an α2-adrenoreceptor antagonist that induces anxiety-like responses in humans and animals [56,57], and reinstates cocaine seeking in monkeys [58], and methamphetamine seeking in rats [52]. Given the importance of stress-mediating systems as motivating components in relapse [39], as well as the evidence of the stress response contributing to cue-induced drug seeking [60], use of yohimbine or other stressor in the extinction-reinstatement model could provide a vital probe into the therapeutic potential of various compounds in methamphetamine-dependent individuals.
Finally, it is worth noting that several studies using the extinction-reinstatement model incorporate a separate experiment using rats trained to respond for food or sucrose pellets in the presence of cues. The compounds found to attenuate reinstatement to methamphetamine seeking were then tested for effects on responding reinforced by food [35,39,47,49] or reinstatement of food-seeking behavior triggered by cues [36]. Measurement of food reinforcement or food seeking is often used in studies of drug-seeking behavior in order to establish specificity of a compound’s effects on drug versus non-drug mechanisms, but the caveat exists that the substrates of drug and food reinforcement heavily overlap [61].

Investigation of the Anti-Reinstatement Potential of Specific Neurochemical Substrates

Dopamine

The characteristic neurobiological effects of methamphetamine are exerted on the dopamine system; as an analogue of amphetamine, it exerts its reinforcing properties via occupation and reversal of the dopamine transporter [62,63]. A well-established consequence of chronic methamphetamine exposure is a depression of brain monoamine levels, where repeated high doses of methamphetamine result in reduced amounts of serotonin and dopamine that persist for several months [64,65]. These observations were confirmed in primates weeks after the completion of high-dose methamphetamine regimens [66] as well as doses comparable to human abuse patterns [67]. Methamphetamine binds to transporter proteins for dopamine, serotonin and norepinephrine, reducing their capability to manage synaptic catecholamine release [62,68,69]. In addition, methamphetamine is internalized by the presynaptic cell and accumulated in synaptic vesicles, where it disrupts the electrochemical gradient required for dopamine sequestration [70]. Consequently, dopamine accumulates in the presynaptic cell and is eventually released into the synapse via reverse dopamine transport [62]. Methamphetamine exposure also results in the formation of reactive oxygen and reactive nitrogen species, contributing to changes in dopamine sequestration and other dopamine-related functional deficiencies [71,72]. Human imaging studies have shown reduced levels of dopamine transporters and D2 receptors in the early stages of methamphetamine withdrawal [73,74], the latter phenomenon having a correlation with post-scan incidence of relapse [75].

The discovery of pharmaceutical compounds that serve to stabilize dopamine function in animals with a history of drug exposure has been a focus of research. In particular, a recent study found the treatment with the D3 receptor antagonist PG01037 attenuated cue-induced reinstatement of methamphetamine seeking as well as methamphetamine reward [76]. The D2 agonist SKF-81297 was found to dose-dependently attenuate both cue- and drug-primed reinstatement, with both effects reversible by pretreatment with the D2 antagonist SCH-23390 [50]. Additionally, the synthetic compound (−)-BPAP, an enhancer of electrically stimulated monoamine release that does not itself release catecholamines, was also found to attenuate cue-induced methamphetamine seeking, presumably by activating D2 receptors, but these effects were not reversed by either SCH-23390 or the D2 agonist amisulpride [50]. Another study also found that pretreatment by SCH-23390 resulted in attenuated methamphetamine-primed methamphetamine seeking, but pretreatment by the D2 antagonist eticlopride failed to exert a comparable effect [77]. This result was consistent with prior observations that eticlopride had no significant effect on self-administration of methamphetamine [78], but is at variance with the anti-reinstatement effects found for eticlopride and other D2 antagonists in cocaine- [79,80] and heroin-seeking behavior [81]. Together, these results exhibit candidate treatments for methamphetamine relapse tailored to act upon dopamine receptor subtypes D1 and D2.

The dopamine receptor family appears to be comprised of prime candidates for investigation with rats given extended access to methamphetamine in order to produce an escalation of daily intake [17]. This increased rate of self-administration is accompanied by enhanced sensitivity to the effects of dopamine receptor ligands, including the antipsychotic aripiprazole, which among its various neurotransmitter actions [82] is a dopamine (D2) receptor antagonist [83], and antagonist of the D1 receptor [84]. In methamphetamine self-administering rats, dopamine transporter deficiencies were only detected the dorsal striatum and forebrain of animals exposed to extended access sessions [85]. Thus, the anti-reinstatement performance of dopamine-stabilizing drugs such as aripiprazole may be significantly altered if the escalation model is incorporated into the experimentation.

Currently best known for its association with the biological mechanisms of pair-bonding and maternal behaviors, [86] the
neuropeptide oxytocin is also thought to inhibit long-term habitual behaviors associated with drug reinforcement by inhibiting the dopaminergic activity of mesolimbic neurons [87]. Recently, systemic injections of oxytocin were shown to reduce levels of methamphetamine self-administration, as well as drug-primed reinstatement of methamphetamine seeking [38].

The drug pergolide, an existing treatment of Parkinson’s disease, is a direct agonist of D₃ and D₂ receptors, as well as a partial serotonin 5-HT₂ receptor antagonist [88]. Administration of pergolide in combination with the serotonin 5-HT₂ receptor antagonist ondansetron prior to extinction training resulted in reduced drug-primed methamphetamine-seeking behavior, but the lack of an extended extinction period (2 days) and subsequent baseline make these data difficult to conclusively interpret as motivational effects [40].

Glutamate

The effects of methamphetamine in the central nervous system extend beyond changes in the dopamine system, and include dramatic increases in the release of other monoamines, including glutamate. Glutamate pathways are ubiquitous throughout the brain and interact with drug-induced dopamine imbalances in a complex fashion involving a variety of glutamate receptor families [89], including links between changes in NMDA function and D₂ receptor activation [90], and between D₁ receptor activation and glutamate responses to psychostimulants [91]. The direct and conditioned reinforcing effects of methamphetamine are also sensitive to glutamate manipulation [92-94], suggesting that potential therapeutic compounds may be developed by targeting glutamate neurotransmission. Moreover, the enthusiasm toward finding glutamate receptor ligands for medication of drug abuse stems from the recently developed links between persistent imbalances of synaptic and extrasynaptic glutamate and the loss of control over drug-seeking behaviors [95,96]. Research on cocaine and alcohol addiction using animal models has definitively tied glutamate mechanisms to reinstatement triggered by cues, drug priming and stress [97].

Untreated drug seeking in cocaine and methamphetamine addiction is characterized by increased synaptic glutamate, but simply reducing glutamate levels by blocking ionotropic receptors is known to produce a range of undesirable side effects including psychotomimesis [98]. Recent research efforts have therefore focused on the manipulation of metabotropic glutamate receptors (mGluRs) to modulate and reduce glutamatergic activities [112]. In a recent preclinical study, chronic administration of modafinil resulted in the attenuation of cue-induced and drug-primed reinstatement [43]. Reinstatement elicited by a return to the self-administration chamber, following extinction training in a different operant chamber [113], was also reduced by modafinil treatment [42]. In addition, the stimulant properties of modafinil did not induce reinstatement to drug seeking [42], inviting the possibility that this drug could relieve some of the debilitating effects of psychostimulant withdrawal and maintain abstinence for an extended period of time [111,114].

Modafinil was also recently investigated in separate groups of male and female rats; to our knowledge representing the only study of gender differences in anti-reinstatement effects pertaining to methamphetamine [115]. Female rats exhibited greater levels of reinstatement of drug seeking after pretreatment by vehicle, were equally sensitive to the attenuating effects of modafinil but were more sensitive to the effects of the neurosteroids all opregnanelone [115]. These results represent initial evidence of neurobiological explanations behind the different methamphetamine use patterns associated with gender [116].

Opioids

Naltrexone is perhaps the best example of a successful treatment for drug relapse emerging from translational research incorporating reinstatement studies involving humans and animals. Naltrexone, a competitive opioid receptor antagonist, has been found to reduce alcohol-seeking in rodents [117,118] and self-reported craving for alcohol in humans [119]. It is currently an approved medication for the treatment of relapse to alcohol consumption in alcoholics, and its potential use as an anti-relapse therapy against other drugs of abuse is of prime interest [120-122]. However, the clinical benefits of this treatment are known to be limited by the lack of compliance in alcoholic patients [123], and its anti-craving effects are markedly reduced in rats physically dependent on alcohol [124]. In rats trained to self-administer methamphetamine, naltrexone treatment effectively reduced subsequent cue-induced drug seeking but not drug-primed seeking [47]. To our knowledge, the anti-reinstatement effects of naltrexone have not yet been tested in rats with a history of methamphetamine self-administration. Furthermore, a regimen of repeated naltrexone injections was found to decrease cue-induced cocaine seeking [125] but has not been tested for cues associated with methamphetamine.

Despite the reported effectiveness of buprenorphine and methadone in attenuating cocaine reinstatement and their clinical availability [126,127], no published reports of opioid receptor-targeting compounds beyond naltrexone have been tested on methamphetamine reinstatement. A recent report on the attenuating effect of buprenorphine on responding to sucrose-associated cues indicates some nonspecific consequences for this treatment [128], but the opioid system remains a relatively unexplored area in the field of methamphetamine craving.

Serotonin

The effects of methamphetamine exposure and dependence on serotonin neurotransmission are well documented [129], making the many receptor subfamilies of this monoamine intriguing targets...
for investigation with the extinction-reinstatement model. Acute administration of methamphetamine results in a dramatic increase in striatal serotonin release [130], and chronic exposure to the drug is accompanied by long-lasting reductions in serotonin production [6,131] and serotonin transporter expression [70]. Several experiments have found that injections of 5-HT\(_1\) receptor antagonists or 5-HT\(_2\) receptor agonists reduce cocaine-seeking behavior elicited by cues, following extensive self-administration and extinction training [132-134]. Treatment with the atypical antidepressant mirtazapine, which has actions on the 5-HT\(_{2A}\), 5-HT\(_1\), histamine and α2-norepinephrine receptors, was found to reduce cue-induced methamphetamine seeking [181]. However, besides the study investigating the 5-HT\(_1\) receptor antagonist ondansetron in combination with a dopamine agonist pergolide that was discussed earlier [40], to date there have been no further investigations of reinstatement-blocking potential of serotonergic compounds in the rat model. Given the regulatory role 5-HT\(_1\) receptors have on the dopaminergic reward- and motivation-mediating pathways of the brain and the evidence linking serotonin function with cocaine-seeking behavior [135], their contribution to methamphetamine seeking would seem to be worth investigating in a model that matches the standard procedures established by the cocaine literature.

In addition to the relative paucity of animal studies, the clinical application of serotonin pharmacology to methamphetamine dependence problems has resulted in mainly negative findings. In a recent study, treatment with the selectively serotonin reuptake inhibitor (SSRI) sertraline resulted in an increased risk for relapse for methamphetamine use [137,138]. In addition to the relative paucity of animal studies, the clinical application of serotonin pharmacology to methamphetamine dependence problems has resulted in mainly negative findings. In a recent study, treatment with the selectively serotonin reuptake inhibitor (SSRI) sertraline resulted in an increased risk for relapse for methamphetamine use [137,138].

**Stress-mediating systems**

A major conceptualization of addiction is that of a stress surfeit disorder, in which dependent individuals experience chronic craving and relapse in response to drug-associated or stressful stimuli [59]. As mentioned earlier, stressful experiences form a plausible trigger for reinstatement to drug-seeking in animals and craving in humans [139,54]. Additionally, reinstatement to psychostimulant-seeking behavior triggered by cues is also mediated by components of the stress response system, including CRF\(_1\) receptors and corticosterone [140]. Both the CRF\(_1\) receptor antagonist CP-154,526 and the glucocorticoid receptor inhibitor ketoconazole were effective in attenuating reinstatement triggered by a small methamphetamine priming injection, but not by drug-paired cues, when systemically administered [39]. However, centrally injected (into the cerebral ventricle) CP-154,526 attenuated cue-induced reinstatement, signaling a critical role for CRF\(_1\) signaling but not corticosterone production for this behavior. Although the rats in this experiment were training in limited-access (2 hr) sessions, the total drug exposure was apparently sufficient to induce withdrawal marked by a negative affective state reversible by CRF\(_1\) antagonism. This is in contrast to cocaine exposure, where the CRF\(_1\) antagonist antalarmin reduced cocaine intake in rats with a history of extended access and cocaine escalation, but was ineffective in changing the behavior of nondependent, short-access rats [141]. More studies focusing on CRF and other substrates of the stress response are needed, but the present results may represent the role of negative affect in methamphetamine-conditioned behaviors [142].

The first drug shown to conclusively reduce operant responding during a stress-induced reinstatement session is the anti-inflammatory drug AV411 (ibudilast), principally known for its analgesic and neuroprotective properties [143,144]. A study utilizing 15 min intermittent footshock and 1 mg/kg methamphetamine priming injection in different cohorts demonstrated that ibudilast significantly reduced reinstatement behavior in both tests [37]. The anti-reinstatement effects of ibudilast were presumably the result of its neuroregulatory actions, which include attenuation of glial activity, production of the growth factor GDNF and the inhibition of phosphodiesterase activity [145]. This compound has no known direct interactions with dopamine, glutamate, opioid, serotonin or cannabinoid receptors, or with dopamine or serotonin transporters [143], and thus represents a distinct target for managing the consequences of methamphetamine exposure on stress systems.

**Nicotine and cannabinoid receptors**

The cannabinoid neurotransmission system is widespread throughout the brain and has been linked with reward processing and drug-seeking activity [146,147]. Not only does the stimulation of endocannabinoid receptors (primarily CB\(_1\) receptors) result in cannabinoid seeking in rats previously trained to self-administer cannabinoid agonists [148], but also elicits drug-seeking in other drug-trained rats as well [149]. Conversely, the CB\(_1\) antagonist rimonabant has been shown to interfere with drug-primed, cue-primed but not stress-elicited reinstatement of various drugs, including cocaine [150]. The stimulation of CB\(_1\) by the drug Δ\(^{2}\)-tetrahydrocannabinol (THC) and blocking of CB\(_1\) by rimonabant were tested for effects on reinstatement of methamphetamine seeking [49]. THC augmented reinstatement elicited by cues combined with 1 mg/kg methamphetamine, but reduced drug-seeking behavior when co-administered with a high priming dose (3.2 mg/kg) of methamphetamine, indicating a modulatory effect on the drug-primed motivational circuits [49]. In contrast, another study failed to show CB\(_1\)-antagonist effects on reinstatement induced by a small priming dose of methamphetamine (0.1 mg/kg) [151]. Although the drugs used in these two conflicting studies were different (rimonabant and AM251, a CB\(_1\) inverse agonist), the limited amount of data does not conclusively support a critical role for CB\(_1\) function in the reinstatement of methamphetamine seeking.

Nicotine has been found to exert protective effects against Parkinson’s-like symptoms associated with methamphetamine toxicity [152]. The contribution of nicotinic acetylcholinergic neurotransmission to methamphetamine-conditioned behavior was investigated in a series of reinstatement tests [35,50]. Systemic injections of nicotine as well as the acetylcholinesterase inhibitor donepezil resulted in suppression of cue- and drug-induced reinstatement of methamphetamine seeking, via selective activation of nicotinic acetylcholine and nor muscarinic receptors. In each case the anti-reinstatement effects were specific to methamphetamine seeking and not food seeking [35]. However, a recent report of nicotine eliciting methamphetamine-seeking in rats with prior exposure to nicotine reinforcement demonstrated that in subjects with a history of exposure to both drugs, nicotine can act as a trigger for reinstatement instead of a therapeutic agent [153]. Considering the extremely high rate of nicotine use among regular methamphetamine abusers [154,155], the possibility of nicotine being utilized as a protective treatment is admittedly difficult to appreciate.

The naturally occurring nicotinic receptor ligand lobeline has been known to decrease methamphetamine-induced stereotypy as well as methamphetamine self-administration [156-158], properties associated with possible dopamine and stimulant effects. Unlike
stimulants, however, lobeline was found not to support self-administration on its own, and also had no effect on drug-primed reinstatement of methamphetamine seeking [41]. Additionally, this compound did not reinstate extinguished methamphetamine seeking or have any observable effect on central dopamine release. Thus, the therapeutic value of lobeline appears to be restricted to the reduction of methamphetamine intake without having abuse potential of its own, rather than preventing relapse of drug craving [41].

Despite the equivocal or negative outcomes in establishing anti-relapse properties of CB₁ ligands and nicotine, the ability of THC or nicotine to induce or augment reinstatement to methamphetamine seeking illustrates an important triggering mechanism. Depending on the time course of exposure and abstinence, neuroadaptative changes induced by chronic nicotine, cannabis, alcohol and other drugs can conceivably exert either protective effects against reinstatement or confer vulnerability to greater methamphetamine seeking. This question remains underinvestigated in the research of not only methamphetamine but also cocaine and other important drugs of abuse [9].

Conclusions

The studies of the anti-reinstatement properties of a large variety of compounds demonstrate that promising candidate treatments for methamphetamine abuse exist across a spectrum of neurobiological substrates. The most developed series of experiments appear to be those concerning modafinil and dopamine receptor ligands, but there are many other promising results to build upon. To date, almost all of the other positive anti-reinstatement findings remain as single published studies. The generally consistent approach in incorporating the extinction-reinstatement model for methamphetamine addiction grants the benefits of standardization and increased comparability of results from different studies, but also besets the theoretical and practical shortcomings of this paradigm. In particular, the reinstatement test is a behavioral interpretation of craving, which in addicts is a subjective response [55]. Self-reports of craving in a laboratory setting have generally been poor predictors of actual relapse among study participants [159,160]. The in-laboratory measurement of craving as a single variable [161] as well as the use of retrospective reports of craving and other triggers of relapse remain controversial [162]. In spite of these problems, the triggers for reinstatement of drug-seeking behavior in the rat bear many similarities to the stimuli that provoke craving in addicts [163-166]. The lack of predictive validity associated with cocaine and methamphetamine reinstatement animal models is primarily due to the fact that clinical studies of treatments have focused on reduction in drug intake among patients and not the maintenance of abstinence [9]. It can also be argued that in vivo functional magnetic resonance imaging studies of human stimulant abusers have adequately demonstrated measurable brain responses to drug priming and drug-associated audiovisual cues that temporally match elevated levels of self-reported craving [167-169]. Though obstacles remain in establishing the extinction-reinstatement model as a fully valid approach to the study of relapse in the minds of all investigators, its flexibility and relevance toward all major drugs of abuse make it a viable strategy for researching the mechanisms of addiction.

The various compounds discussed above could be tested using extensions of the extinction-reinstatement model, including stress-induced reinstatement tests, incorporation of the escalation model to evaluate the effects of physical dependence, and inclusion of female rats to begin to assess the impact of gender on methamphetamine craving. Adaptations of the stress response incorporate a large number of neurotransmitter and neuropeptide systems, including most of those reviewed above and alteration of stress-mediating brain circuits thought to be critical in the transition from habitual drug use to drug dependence [32,59]. Additionally, the scope of investigation of anti-relapse targets can be expanded beyond the existence of available ligands by utilizing the extinction-reinstatement model in transgenic mice [170,171].

An alternative procedure for assessing drug-motivated behavior is testing for the reinstatement of extinguished conditioned place preference (CPP), [172,173]. Rats are first exposed to two neutral environments (distinguished from each other by olfactory, visual and/or tactile cues) in separate repeated conditioning sessions, with one environment being paired with injections of methamphetamine and the other environment paired with a non-drug state (i.e., saline). Following sufficient conditioning, the rats, when given an opportunity to choose between the environments in a non-drug state, express a preference toward the methamphetamine-paired environment. This CPP behavior is then extinguished by repeated extinction sessions where the rats are exposed to both environments without methamphetamine. CPP toward the previously drug-paired environment is then reinstated by a priming injection of methamphetamine, providing an indirect assessment of the persistent reinforcing effects of methamphetamine. Drug-induced reinstatement of methamphetamine CPP has been shown to be attenuated by pretreatment with the nitrous oxide inhibitor 7-nitroindazole [174] or the GABA transaminase inhibitor vigabatrin [175] in rats, and by bee venom in mice [176]. Though it has been utilized infrequently for methamphetamine research [177] and concerns persist about the standardization of its procedure [178], reinstatement of CPP offers an alternative strategy for investigation into the biological substrates of conditioned methamphetamine seeking.

Finally, it is worth noting that the compounds evaluated so far represent a partial overlap of the total number of drugs actively being researched in clinical studies for the same ultimate purpose [179]. The current enthusiasm for “repurposing” medications that are currently researched in clinical studies for the same ultimate purpose [179]. The current enthusiasm for “repurposing” medications that are currently approved for other clinical uses [180] has potential for motivating reinstatement experiments directly relevant to the scope of available treatments.

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