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Review

Pharmacologically-mediated reactivation and reconsolidation blockade of the psychostimulant-abuse circuit: A novel treatment strategy

Tong H. Lee[a,*], Steven T. Szabo[a], J. Corey Fowler[d], Paolo Mannelli[a], O. Barry Mangum[e], Wayne F. Beyer[f], Ashwin Patkar[a], William C. Wetsel[a,b,c]

[a] Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710, United States
[b] Department of Cell Biology, Duke University Medical Center, Durham, NC 27710, United States
[c] Department of Neurobiology, Duke University Medical Center, Durham, NC 27710, United States
[d] Duke Clinical Research Institute, Duke University Medical Center, Durham, NC 27710, United States
[e] Duke Clinical Research Unit, Duke University Medical Center, Durham, NC 27710, United States
[f] Duke Translational Research Institute, Duke University Medical Center, Durham, NC 27710, United States

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ABSTRACT

Psychostimulant abuse continues to present legal, socioeconomic and medical challenges as a primary psychiatric disorder, and represents a significant comorbid factor in major psychiatric and medical illnesses. To date, monotherapeutic drug treatments have not proven effective in promoting long-term abstinence in psychostimulant abusers. In contrast to clinical trials utilizing monotherapies, combinations of dopamine (DA) agonists and selective 5-HT_3, $5HT_{2A/2C}$, or NK_1 antagonists have shown robust efficacy in reversing behavioral and neurobiological alterations in animal models of psychostimulant abuse. One important temporal requirement for these treatments is that the 5-HT or NK_1 receptor antagonist be given at a critical time window after DA agonist administration. This requirement may reflect a necessary dosing regimen towards normalizing underlying dysfunctional neural circuits and "addiction memory" states. Indeed, chronic psychostimulant abuse can be conceptualized as a consolidated form of dysfunctional memory maintained by repeated drug- or cue-induced reactivation of neural circuit and subsequent reconsolidation. According to this concept, the DA agonist given first may reactivate this memory circuit, thereby rendering it transiently labile. The subsequent antagonist is hypothesized to disrupt reconsolidation necessary for restabilization, thus leading progressively to a therapeutically-mediated abolishment of dysfunctional synaptic plasticity. We propose that long-term abstinence in psychostimulant abusers may be achieved not only by targeting putative mechanistic pathways, but also by optimizing drug treatment regimens designed to disrupt the neural processes underlying the addicted state.

Contents

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Box 3870, Duke University Medical Center, Durham, NC 27710, United States. Tel.: +1 919 684 4374; fax: +1 919 681 8369.
E-mail address: tong.lee@duke.edu (T.H. Lee).

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1. Psychostimulant addiction

Psychostimulant abuse and dependence continue to exert profound socioeconomic, legal and medical problems throughout the world. In the United States (US), a recent survey (SAMHSA, 2009) estimated that 49.4 million or 21.2% of individuals aged 12 years or older had used cocaine or methamphetamine (METH) during their lifetime. Among ~6.1 million US residents who had used these two drugs in the past year, 722,000 persons had used cocaine for the first time, while the number for METH was 95,000 (SAMHSA, 2009). Treatment program admissions in 2007 for persons with primary cocaine or METH abuse accounted for 21% of 1,817,517 total admissions (SAMHSA, 2008), while psychostimulant-related emergency-department visits accounted for 33.9% of visits due to illicit drug use (SAMHSA, 2010). Compared to the US, a recent report by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2010) estimated that 14 and 12 million Europeans used cocaine and amphetamines (i.e., amphetamine and METH) at least once in their lifetime, respectively. Among these users, 4 and 2 million individuals used the respective drugs during the past year. In contrast to North American and European countries, amphetamines, especially METH, represent the most commonly abused psychostimulant in the Pacific Rim countries including Japan, South Korea and Australia (Darke et al., 2007).

Psychostimulant dependence is not only a primary psychiatric disorder but also represents a significant comorbid factor for several major psychiatric disorders (Regier et al., 1990). For example, schizophrenic patients have higher degrees of psychostimulant abuse (15–60%) than the general US population (Miller and Tanenbaum, 1989; Dixon et al., 1991; Volkow, 2009). While an increased rate of psychostimulant abuse may partly represent an attempt to overcome aversive symptoms or treatment-related side-effects (e.g., "self-medication" hypothesis) or an increased psychostimulant sensitivity due to "dopaminergic supersensitivity" induced by chronic antipsychotic treatment (Khantzian, 1985; Gawin and Kleber, 1986; LeDuc and Mittleman, 1995; Fukushiro et al., 2007), more recent studies have indicated potential mechanistic overlaps between psychostimulant abuse and other primary psychiatric disorders (see Volkow, 2009). Psychostimulants, especially the amphetamine derivatives, may induce psychotic states in mentally ill or vulnerable individuals (Connell, 1958; Ellinwood, 1968; Angrist and Gershon, 1970; Janowsky and Risch, 1979; Mahoney et al., 2008), and they may adversely affect the clinical course of psychiatric disorders (Janowsky and Davis, 1974; Drake and Wallach, 1989; Glasner-Edwards et al., 2010). Effective prevention and treatment strategies against psychostimulant abuse should facilitate overall management and improvement of prognosis for patients diagnosed with various psychiatric disorders. With respect to non-psychiatric sequelae, intravenous drug use and drug-induced behavioral disinhibition increases the risk of acquiring immune deficiency syndromes, as well as hepatitis C, sexually-transmitted diseases, and various cardiovascular ailments (Gonzales et al., 2006; Colfax and Shoptaw, 2005; Cruickshank and Dyer, 2009).

2. Current state of pharmacotherapies for psychostimulant abuse

To date, more than two dozen medications have been tested in clinical trials as monotherapies against psychostimulant abuse. These drugs include clinically-available psychostimulants (e.g., dextroamphetamine or methylphenidate), selective serotonin reuptake inhibitors (e.g., fluoxetine) and other antidepressants (e.g., mirtazapine), full or partial DA agonists (e.g., pergolide, aripiprazole), atypical antipsychotic agents (e.g., risperidone), γ-aminobutyric acid (GABA) receptor agonists (e.g., gabapentin and baclofen), the analeptic modafinil. However, only a few have shown limited treatment efficacy, and none are FDA-approved for this indication. Bupropion, an antidepressant and smoking cessation aid, *n*-acetylcysteine, *d*-cycloserine, and the antiepileptic topiramate are also currently undergoing clinical investigations. Current medication development efforts for psychostimulant abuse have been recently reviewed (see Elkashef et al., 2008), and additional ongoing clinical trials can be found on the clinicaltrials.gov website (http://www.clinicaltrials.gov/). In addition to pharmacological treatments, cocaine vaccines have recently shown encouraging results (Kinsey et al., 2010), although this immunization strategy is still limited by the frequent dosing needed for efficacy, as well as a need for implementation of a clear vaccination policy (Hall and Gartner, 2011).

A potential explanation for unsatisfactory outcomes in monotherapeutic strategies, including psychostimulant vaccines, may be that these treatments are primarily designed to provide a "palliative" intervention, rather than directly targeting the dysfunctional neural processes underlying chronic psychostimulant use. Psychostimulant substitutes or "psychostimulant antagonists" are administered primarily to prevent the craving or reinforcing effects of the drug. These strategies may exert minimal effects on dysfunctional neurobiological states that underlie the continued psychostimulant use and vulnerability towards relapse in the addicted brain. Pathophysiologically-directed therapies, on the other hand, are likely to lead to an enhanced therapeutic outcome because they may reverse dysfunctional neurobiological processes and restore normal neural functions and behaviors. The present review describes a preclinical treatment strategy, which may lead to a more effective intervention and therapeutic outcome through the use of a temporally-spaced combination of two clinically-available drugs. Readers seeking more detailed discussions of potential mechanisms underlying psychostimulant abuse per se are referred to a comprehensive collection of reviews recently published in Neuropsychopharmacology (Vol. 33, January, 2008) as well as that by Koob and Volkow (2010).

3. Efficacy of combination treatment regimen in animal models

3.1. Overview

In contrast to sub-optimal results from monotherapeutic clinical trials, drug combination treatments have consistently shown to reverse behavioral and neurobiological alterations in behavioral sensitization and self-administration models of human psychostimulant abuse. Overall, we have demonstrated that a DA agonist in combination with a selective 5-HT_3, $5HT_{2A/2C}$, or NK-1 receptor antagonist can consistently and robustly reverse *both* behavioral and neurobiological alterations in animal models of psychostimulant abuse (Davidson et al., 2002b,c, 2004, 2007; Zhang et al., 2007; Bhatia et al., 2011). When these combinations are administered under a specific dosing regimen for 5–7 consecutive days, these treatments (a) reverse previously-established cocaine or METH

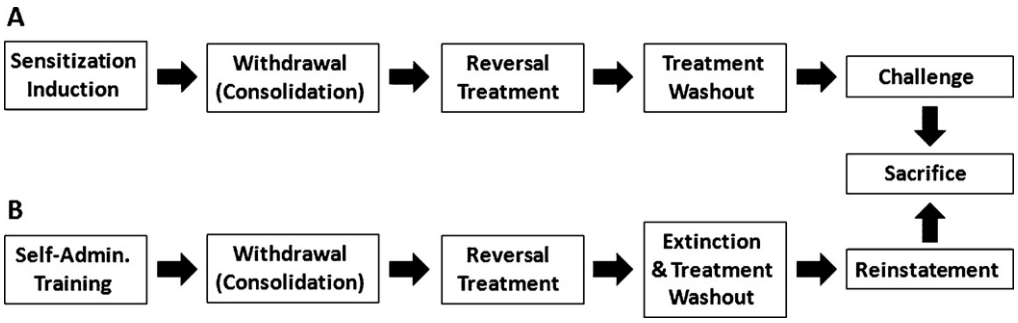

Fig. 1. (A) Behavioral sensitization paradigm. Sprague-Dawley rats are treated with either cocaine or METH to induce sensitization and withdrawn for 7–14 days to establish behavioral sensitization (consolidation). Subsequently, they are given a control or agonist/antagonist combination treatment for seven days, followed by a second withdrawal period to wash out the treatment drugs. On the acute challenge day, cocaine- and METH-sensitized animals are acutely challenged with their respective sensitization drug, and are sacrificed on the following day for neurobiological marker measurements. Psychostimulants themselves (cocaine and METH) and pergolide have been used as DA agonists, while ondansetron (5-HT_3), ketanserin/mianserin (5-$HT_{2A/2C}$), clozapine (5-HT_3, 5-$HT_{2A/2B}$ and other receptor subtypes) and WIN51708 (NK1) are antagonists that have shown efficacy in combinations with the agonist. (B) Drug-induced self-administration (SA) reinstatement paradigm. Similar to behavioral sensitization, rats are trained to nose-poke for cocaine or METH, withdrawn establish SA (consolidation), and subsequently treated with a combination treatment. Upon the treatment completion, rats undergo extinction followed by drug-induced reinstatement procedure. Tissue samples are collected one day after the last reinstatement testing. Combinations of pergolide and ondansetron have shown to reduced drug-induced reinstatement.

behavioral sensitization; (b) attenuate self-administration under progressive ratio and drug-induced reinstatement paradigms; and (c) normalize changes in associated neurobiological markers. The DA agonists tested in the combination treatments include psychostimulants themselves (e.g., cocaine) and the "anti-Parkinsonian" agent pergolide. It is noted that pergolide is no longer available clinically due to its propensity to induce heart valvulopathy (Schade et al., 2007). The 5-HT agents that have shown preclinical efficacy include the 5-HT_3 antagonist ondansetron and the 5-HT_2 antagonist ketanserin, while the NK-1 antagonists include WIN51708. The 5-HT_3 antagonist ondansetron is used in clinics as an antiemetic agent, as is the recently-approved NK1 receptor antagonist aprepitant. Fig. 1 provides a brief overview of the sensitization and self-administration paradigms used in the above studies, and Table 1 presents selected neurobiological changes associated with established cocaine sensitization, which are normalized by a combination of pergolide and ondansetron administered under the dosing regimen described in the present review.

3.2. Reversal of behavioral sensitization

Psychostimulant behavioral sensitization following repeated intermittent exposure in animals is characterized by progressive increases in behavioral responsivity to these drugs. Sensitization is considered a model of psychostimulant abuse and progression into compulsive use, especially when the drug is administered in dosing patterns that are designed to mimic those observed in compulsive high-dose human abusers (see Davidson et al., 2007; Steketee and Kalivas, 2011). Once consolidated through a few days of drug withdrawal, the increased behavioral responsivity to psychostimulants is maintained even after long-term withdrawal. This long-term maintenance suggests that a stable dysfunctional "memory" is formed, and may underlie the remarkable relapse vulnerability in human abusers even after prolonged abstinence (Gawin and Ellinwood, 1988; Taylor and Gold, 1990; Shalev et al., 2002). Notably, sensitization has been accepted to model neuroadaptations associated with addiction to psychostimulant and other drugs of abuse (see Robinson and Berridge, 2008).

We first have demonstrated that consolidated behavioral sensitization in rodents can be reversed if the sensitized animals are treated daily with cocaine injections, and if each of these injections is followed 3.5 h later with an antagonist to 5-HT_3 (e.g., ondansetron) or 5-HT_2 (e.g., ketanserin) receptors (Davidson et al., 2002b,c, 2004). Behavioral efficacy of these combined DA agonist/5-HT antagonist regimens is especially striking considering that psychostimulants given alone during the same period further increases, rather than decreases, behavioral sensitization (Davidson et al., 2002a). Daily treatment with ondansetron alone is ineffective in reducing *consolidated* behavioral sensitization (Davidson et al., 2002c) although this monotherapy can reduce the sensitization expression – if it is administered during the first 5 days of cocaine withdrawal, before a full consolidation of behavioral sensitization (King et al., 2000). Additional 5-HT antagonists that have been shown to reverse cocaine sensitization when given after daily

Table 1
Changes in the protein expression levels of selected neurobiological markers in the prefrontal cortex (PFC) and nucleus accumbens core (NAc Core) that are associated with consolidated cocaine sensitization and self-administration (S-A). Pergolide/ondansetron combination treatment normalizes these changes.

	PFC	NAc Core	References
NR2B NMDA receptor subunit	NC	NC	Zhang et al. (2007)
NR2B Tyr^{1472} phosphorylation	NC	(−)	Zhang et al. (2007)
GluR1 AMPA receptor subunit	NC	NC	Zhang et al. (2007)
GluR1 Ser^{831} phosphorylation	NC	NC	Zhang et al. (2007)
GluR1 Ser^{845} phosphorylation	(+)	(+)	Zhang et al. (2007) and Chen et al. (2010)
GluR1 Ser^{845} phosphorylation (S-A)	(+)	(+)	Zhang et al. (2007) and Chen et al. (2010)
Brain-derived neurotrophic factor	(+)	(+)	Unpublished results
Integrin-linked kinase	(+)	(+)	Chen et al. (2008) and unpublished results
Protein kinase B (Akt)	NC	NC	Chen et al. (2008) and unpublished results
Akt Thr^{308} Phosphorylation	NC	NC	Unpublished results
Akt Ser^{478} Phosphorylation	(+)	(+)	Chen et al. (2008) and unpublished results
Protein kinase C (PKC) ζ	N/D	(+)	Chen et al. (2007)
PKC ζ (S-A)	N/D	(+)	Unpublished results
PKC ζ Thr^{410} Phosphorylation	N/D	(+)	Chen et al. (2007)

(+), increased vs. non-sensitized animals; (−), decreased vs. non-sensitized animals; NC, no change; N/D, not determined.

cocaine administration include clozapine (5-HT_3, 5-$HT_{2A/2B}$ and other receptor subtypes), mianserin (5-$HT_{2A/2C}$), and WIN51708 (NK1; Davidson et al., 2002b, 2004). It is important to reiterate that the desired reversal of behavioral sensitization is achieved if, and only if, the antagonist is given after, but not before or simultaneously with the agonist (Davidson et al., 2002c).

Reversal of behavioral sensitization can be also achieved with combination treatment if the psychostimulants themselves are substituted with pergolide and followed 3.5 h later with ondansetron or ketanserin (Zhang et al., 2007; Davidson et al., 2007; Bhatia et al., 2011). Similar to that of psychostimulant treatments alone, daily treatments with pergolide alone are ineffective (Zhang et al., 2007; Davidson et al., 2007; Bhatia et al., 2011). In fact, pergolide alone tends to further increase the behavioral sensitivity to psychostimulants (Bhatia et al., 2011). This cross-sensitizing effect of chronic pergolide monotherapy may partially account for the variable therapeutic outcomes of this therapy with cocaine abusers (Malcolm et al., 2000; Levin et al., 1999). Moreover, in a controlled clinical study, pergolide has also been shown to induce cocaine "craving" in abstinent cocaine abusers (Haney et al., 1998). In contrast to responsivity to cocaine or METH challenge, agonist/antagonist combination treatments do not alter either pre- or post-challenge "baseline" activity levels. Together with the normalization of sensitization-associated neurobiological markers (Table 1), these observations suggest that their effects on sensitized animals are likely to represent a true treatment effect, rather than nonspecific behavioral inhibition (e.g., lethargy) or a conditioned "hypolocomotor" response induced by the prior combination treatment. Either of these effects could "mask" sensitization following acute drug challenge (e.g., a new extinction memory competing with the expression of consolidated memory).

3.3. Attenuation of self-administration

In addition to behavioral sensitization, ondansetron given at a critical time window *after* daily cocaine self-administration sessions decreases the progressive ratio break-point measured on the next day, when the antagonist should be completely eliminated from the body (Davidson et al., 2002c). It should be noted that the break-point under progressive ratio paradigms is considered a measure of the "willingness to work" toward obtaining a given reinforcer by the animal, where a higher break-point signifies higher willingness. By contrast, a reduced break-point in the above preclinical studies suggests that combined cocaine (self-administration) and subsequent ondansetron treatment may be effective in reducing drug use in active cocaine abusers. Similarly, in an animal model of relapse, combined pergolide-ondansetron treatment after acquisition of a stable self-administration pattern has been demonstrated to attenuate subsequent cocaine- or METH-induced reinstatement under an extinction and reinstatement self-administration paradigm (Davidson et al., 2007). This attenuation suggests that targeted treatment of abstinent psychostimulant abusers may be effective in preventing future relapses that frequently occur upon drug re-exposure (Gawin and Ellinwood, 1988).

4. Role of acute psychostimulant withdrawal in maintaining psychostimulant abuse

Traditional facets of psychostimulant addiction have focused on positive reinforcing effects of these agents with molecular and neurochemical changes in critical brain circuits such as the mesoaccumbens DA and corticoaccumbens glutamate pathways. In contrast, the DA agonist/5-HT antagonist combination treatment described in the present review is based largely upon a hypothesis that repeated induction of aversive responses during psychostimulant withdrawal, rather than positive drug rewarding effects, plays a key role in long-term maintenance of relapse vulnerability in compulsive psychostimulant abuse (Koob and Le Moal, 2001; Davidson et al., 2002c; Zhang et al., 2007; Fukushiro et al., 2011; see D'Souza and Markou, 2010 for detailed discussion on psychostimulant withdrawal). Psychostimulant withdrawal is often associated clinically with dysphoria, anhedonia, anergia and other depressive symptoms (Gawin and Ellinwood, 1988; Ellinwood and Lee, 1989; Foltin and Fischman, 1997; Newton et al., 2004; Leventhal et al., 2008). The intensity of the aversive withdrawal symptoms is correlated with increased subjective "high" induced by subsequent cocaine challenges (Newton et al., 2003; Sofuoglu et al., 2003), and is a strong predictor of poor treatment response (Mulvaney et al., 1999; Kampman et al., 2001). Consistent with these "stress-associated" symptoms, basal activity and stressor-induced activation of the hypothalamic–pituitary–adrenal axis (HPA) are exaggerated during cocaine withdrawal in both animals and humans (Sarnyai et al., 1998; Contoreggi et al., 2003; Mantsch et al., 2007). Furthermore, stress-induced HPA activation shares similar facets to withdrawal symptoms from psychostimulant abuse, and is predictive of cocaine relapse outcomes (Sinha et al., 2006).

The first few days of withdrawal from chronic psychostimulant administration in animals are associated with time-dependent behavioral and neurobiological changes. Pharmacological interference during this early withdrawal phase can prevent the consolidation of long-term behavioral and neurobiological alterations (King et al., 1998; Lee et al., 1999; Li et al., 2000). Furthermore, a spectrum of analogous behavioral stress measures (e.g., ultrasound vocalization) has been reported in animals within days of cocaine withdrawal (Barros and Miczek, 1996; Mutschler and Miczek, 1998; Costall et al., 1990; Fung and Richard, 1994; Koeltzow and White, 2003). Various terms such as "allosteric dysregulation" or "acute withdrawal" have been used to describe aversive neurobiological processes, which characterize acute psychostimulant withdrawal and may contribute to the maintenance of long-term psychostimulant sensitization and abuse (Koob and Le Moal, 2001; Davidson et al., 2002c; D'Souza and Markou, 2010). Interestingly, earlier studies by Kuribara (1994, 1995) demonstrated that administration of D_1 or D_2 antagonists 3 h after METH administration inhibited sensitization induction in rodents, thus suggesting that acute withdrawal may also play an important role in the development of psychostimulant abuse.

The putative role of repeated acute psychostimulant withdrawal in maintaining chronic psychostimulant abuse forms the hypothetical basis for the sequential DA agonist/5-HT antagonist combination regimen. Thus, a psychostimulant or psychostimulant substitute (e.g., pergolide) sharing a similar pharmacological profile with cocaine or METH is first given *therapeutically* to simulate the "drug-on" state (i.e., reactivation of the stable dysfunctional memory). An acute withdrawal state ensues with agonist clearance that can be subsequently blocked with a 5-HT_3, 5-$HT_{2A/2C}$, or NK-1 receptor antagonist given 3.5 h after agonist administration (Davidson et al., 2002a, 2004). The choice of antagonist is based on the significant roles that 5-HT_3, 5-$HT_{2A/2C}$, or NK-1 receptor subtypes play in various responses such as anxiety, psychosis, nociception, and cognition (Barnes et al., 1990; Grant, 1995). Ondansetron and other 5-HT_3 receptor antagonists, as well as, NK-1 antagonists are clinically approved as antiemetic agents for their "anti-aversive" effects. Ondansetron has also shown to be useful in the treatment of alcohol withdrawal (Johnson, 2010). By comparison, drugs with 5-HT_2 receptor affinity have been used in the treatment of anxiety disorders, obsessive compulsive disorder, and major depression (de Leeuw and Westenberg, 2008; Landén and Thase, 2006; Kent, 2000). While localization of the pharmacological

action of these combination treatments awaits additional investigation, the prefrontal cortex (PFC) may be a major site of action for the effects of combination treatments. Thus, the PFC may provide key modulations of consolidated psychostimulant sensitization and self-administration through the corticostriatal glutamate pathway and projection to the ventral tegmental area via the laterodorsal and pedunculopontine tegmetum areas (see Steketee and Kalivas, 2011). Importantly, distinct distributions of 5-HT_{2A} and 5-HT_3 receptors and substance P (neurotransmitter for NK-1 receptors) have been demonstrated in the PFC (Jakab et al., 1997; Jakab and Goldman-Rakic, 2000). Although elucidation of specific "mechanisms" underlying the efficacy of 5-HT and NK-1 antagonists in the combination regimen awaits further investigation, it is interesting to note that extracellular and intracellular calcium signaling through receptor channels (5-HT_3) or "second messenger systems" (5-HT_2 and NK-1 receptors) play major roles in various biological processes including synaptic plasticity (see Berridge et al., 2003 for review).

The hypothesis that all of the above antagonists may specifically act upon agonist-induced withdrawal states to reverse the consolidated psychostimulant abuse memory is supported by the findings that these agents, when used alone, have minimal efficacy in reversing *consolidated* behavioral alterations in animal models of psychostimulant abuse. Heuristically, repeated therapeutic induction and blockade of psychostimulant withdrawal effects may provide a means to disassociate previously established relationships between the acute and aversive withdrawal effects of psychostimulants with that of long-term synaptic dynamics. This dissociation, in turn, may underlie the long-term maintenance of abuse patterns in chronic psychostimulant abusers. Therefore, the rationale for agonist administration employed in the combination-treatment approach contrasts that of "typical" DA agonist treatments, which simply seek to provide positive "drug-on" effects or to induce and maintain tolerance through chronic agonist administration (Ellinwood et al., 2002).

5. Clinical data on the efficacy of ondansetron monotherapy

The National Institute on Drug Abuse (NIDA) has conducted multi-center clinical trials to determine the efficacy of ondansetron monotherapy in maintaining abstinence in cocaine and METH abusers (Johnson et al., 2006, 2008). For cocaine abusers, the 5-HT_3 antagonist (4 mg/kg, b.i.d.) significantly reduced trial dropout rates and improved cocaine abstinence as verified by negative urine screening results (Johnson et al., 2006). Notably, the greatest treatment responses were observed in abusers who had the highest number of cocaine-positive urine samples before entering the trial, suggesting that this treatment exerted higher efficacy in subjects who had the highest frequencies of drug use. This positive correlation between the estimated pre-treatment level of cocaine use and the treatment response contrasts with those reported for most of the other treatments (e.g., modafinil; Anderson et al., 2009). These treatments were essentially more efficacious in cocaine users with low to moderate levels of dependence. Due to active cocaine use by these subjects, it could be hypothesized that the treatment-responsive subgroup may have been surreptitiously subjected to the aforementioned DA agonist/5-HT antagonist combination treatment (self-administered cocaine and ondansetron) and thus showed a positive treatment response. Since ondansetron was administered twice a day in this study and because the half-life of cocaine is 60–90 min in humans (Jeffcoat et al., 1989), many of these subjects may have frequently experienced 5-HT_3 blockade during the acute cocaine withdrawal period. In this regard, it should be recalled that neither consolidated behavioral sensitization nor self-administration can be reversed with ondansetron treatment alone (Davidson et al., 2002c).

In contrast to cocaine, ondansetron monotherapy was not effective for METH abusers (Johnson et al., 2008). While there are several potential reasons for this negative result (e.g., sub-optimal ondansetron doses, etc.), a major difference between effects of ondansetron on cocaine and METH abusers may relate to the much longer half-life of METH, being 6–24 h in humans (Cho et al., 2001) as compared to 60–90 min for cocaine (Jeffcoat et al., 1989). We hypothesize that the longer METH half-life may have resulted in a much narrower therapeutic time-window for the prescribed ondansetron to be taken during the time of acute METH withdrawal. Under such conditions, it is unlikely that ondansetron-mediated 5-HT_3 blockade would have occurred during the period of "reconsolidation" of the addiction memory in the course of acute METH withdrawal. These considerations provide further rationale for the proposed regimen-dependent DA agonist/5-HT antagonist treatments, whereby *both* the reactivation of the addiction circuit and blockade of its reconsolidation could be *therapeutically controlled* for disruption of the consolidated dysfunctional memory.

6. Neural basis of combination treatment efficacy

Various neuropsychiatric disorders are increasingly considered as a consolidated form of maladaptive synaptic plasticity (Kreitzer and Malenka, 2008; Pierce and Vanderschuren, 2010; Lewis and González-Burgos, 2008; Pittenger and Duman, 2008). Accordingly, treatment-mediated normalization of these neuroplastic changes may be expected to lead to a successful therapeutic outcome (Centonze et al., 2005). As illustrated in Fig. 2, chronic psychostimulant abuse can be also conceptualized as a consolidated (stable) form of dysfunctional memory with associated neurobiological changes (see Table 1), which is maintained by repeated cycles of reactivation and reconsolidation (see Centonze et al., 2005 for an overview on reconsolidation inhibition and extinction in psychiatric treatments). In untreated psychostimulant abusers, the stable memory could be reactivated by exposure to various stimuli such as psychostimulants themselves ("drug tasting," unconditioned stimulus), environmental cues associated with drug use (e.g., drug paraphernalia or being near a "crack house," conditioned stimuli) or "stress" (Jaffe et al., 1989; Childress et al., 1999; Sinha, 2001; Sinha et al., 2006), thus contributing to drug taking behaviors (i.e.,

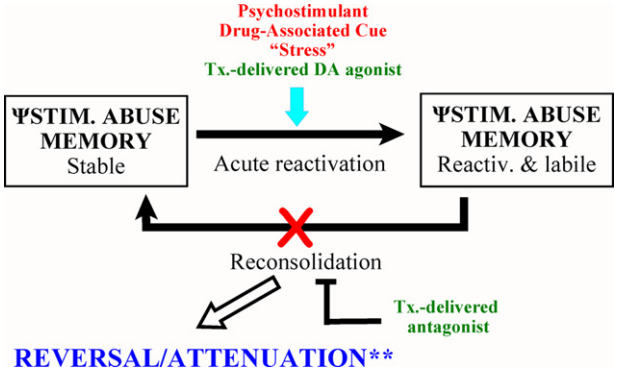

Fig. 2. Hypothesized therapeutic erasure of consolidated psychostimulant (ψSTIM) abuse memory. In untreated psychostimulant abusers, the stable memory is reactivated by exposure to various stimuli such as psychostimulants themselves, environmental cues associated with drug use or "stress" (arrow). Unless interfered with, the reactivated memory becomes reconsolidated during withdrawal. A therapeutically-delivered DA agonist is also hypothesized to reactivate the consolidated psychostimulant abuse memory. The transiently-reactivated circuit is labile and can be disrupted by delayed administration of a 5-HT_3, 5-$HT_{2A/2C}$ or NK-1 antagonist that blocks reconsolidation (×). This reconsolidation blockade leads to "erasure" of the dysfunctional memory (open arrow).

relapse). Unless interfered with, reactivated memory is expected to become reconsolidated during withdrawal (e.g., "crash").

As discussed in Centonze et al. (2005), treatment strategies which can disrupt or erase the established psychostimulant-abuse memory and, thereby, normalize the underlying neurobiological changes in *controlled clinical settings* may lead to successful therapeutic outcomes in chronic psychostimulant abusers. Within this context, we hypothesize that a DA agonist acting as a psychostimulant substitute therapeutically reactivates the consolidated psychostimulant abuse memory to render it transiently labile (Fig. 2). An antagonist given 3.5 h after the agonist (reconsolidation period) disrupts the circuit reconsolidation that is required for memory restabilization. According to this model, psychostimulant replacement through DA agonist monotherapy may be expected only to reactivate the memory, which would subsequently undergo a normal reconsolidation process. In contrast, a "psychostimulant antagonist" given alone may only prevent reactivation of the abuse circuit so that consolidated circuit remains in its original state, thereby abrogating therapeutically-mediated memory reactivation that is prerequisite for a successful treatment outcome. In addition to exposure to psychostimulants or substitutes, exposure to various conditioned stimuli associated with drug use may also reactivate the consolidated dysfunctional memory (Fig. 2). In fact, reactivation and reconsolidation processes has been most extensively investigated within the context of associations between conditioned and unconditioned stimuli (e.g., fear conditioning, drug-associated cues, etc.; see Nader and Hardt, 2009 for review). Several preclinical studies have now demonstrated that, similar to drug-induced reinstatement of self-administration, cue-induced reinstatement can be abolished by blocking reconsolidation (Lee et al., 2005; Bernardi et al., 2007; Kelley et al., 2007; Sadler et al., 2007; Fricks-Gleason and Marshall, 2008). In humans, a clinical study on effects of combined cue-exposure and propranolol on "memory for cocaine craving" has been completed (NCT00830362, clinicaltrials.gov). This nonselective beta-adrenergic receptor antagonist, which is used for treatment of cardiovascular disorders (e.g., hypertension, angina pectoris) as well as situational or performance anxiety, may be hypothesized to block the reconsolidation of the cue-reactivated memory. It is remarkable that, similar to the time interval between DA agonist and ondansetron, the reconsolidation of cue-induced reinstatement of cocaine self-administration has been reported to be susceptible to protein synthesis inhibitors within 4–6 h after cue exposure (Lee et al., 2006), indicating that a key temporal window after drug or cue exposure may be the period of memory reconsolidation requiring new protein synthesis. It may be interesting to hypothesize that a 5-HT or NK-1 antagonist might interfere with the new protein synthesis via their effects on Ca^{2+}-dependent transcriptional and/or translational events (see Section 4).

The combination pharmacotherapeutic approach reviewed herein is conceptually similar to the memory reactivation–degradation model that is being applied to other psychiatric disorders such as post-traumatic stress disorder (see Donovan, 2010). Furthermore, a recent human study has reported that disruption of the reconsolidated fear-conditioned memory can be best achieved when the experimental intervention interfering with reconsolidation is delivered ~3 h after the reactivation cue (Schiller et al., 2010). These considerations suggest that a *critical temporal window of opportunity exists for therapeutic "erasure"* of the dysfunctional memory associated with psychostimulant abuse. It should be also considered that even after a successful therapeutic outcome, genetic and/or environmental predispositions may render many individuals at an increased risk to "reacquire" psychostimulant addiction. Thus, a comprehensive strategy against chronic, repeated psychostimulant abuse should include therapeutic measures designed to prevent reestablishment of dysfunctional "psychostimulant memory."

7. A proof-of-concept clinical trial

A translational proof-of-concept Phase II clinical study sponsored by NIDA (NCT01377662, clinicaltrials.gov) is ongoing to determine the efficacy of a combination of immediate-release methylphenidate as the DA agonist ("psychostimulant substitute") and a novel delayed, pulsatile-released ondansetron formulation for treatment of psychostimulant abuse. In normal healthy volunteers, *simultaneous* oral administration of the two drugs leads to a peak separation of ~4 h with minimal evidence of pharmacokinetic or pharmacodynamic drug–drug interactions (NCT01290276, clinicaltrials.gov). Ondansetron was selected for the formulation development and the clinical trials based on the considerations that this antagonist: (1) has been the most extensively characterized in our preclinical models; (2) has been used in clinical practice with minimal side effects; and (3) has shown efficacy in selected clinical studies in reducing alcohol or cocaine, but not METH use (Johnson et al., 2006, 2008; Johnson, 2010). Finally, the ready availability of generic ondansetron provides a practical advantage for expediting the development and potential approval of novel temporally-released formulations. In addition to clinical tools (e.g., Cocaine Selective Severity Assessment), functional magnetic resonance imaging is being used to assess the treatment outcome in abstinent cocaine and/or methamphetamine abusers residing in a local residential treatment facility.

8. Summary

Under the combination treatment regimen described in this review, the consolidated psychostimulant-abuse circuit is repeatedly reactivated and rendered labile by daily administration of a clinically-available psychostimulant or a psychostimulant substitute. Subsequent administration of a 5-HT_3, 5-HT_2, or NK-1 antagonist within a critical time window, in turn, disrupts reconsolidation and restabilization of the addiction circuit. Such a process-targeting treatment may reverse the underlying neurobiological processes that maintain the psychostimulant abuse and thus may offer the potential for a more effective intervention, rather than palliative treatment strategies. Sequential or programmed administration of two drugs at a fixed time-interval to target reactivation and reconsolidation of psychostimulant-abuse memory circuit is a novel example of targeting a critical time-window to achieve the desired therapeutic outcome.

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Contributors

Dr. Lee wrote the initial draft and Dr. Szabo was responsible for integrating all co-authors feedback. All authors provided feedback on the manuscript and approved the final version.

Conflict of interest

Drs. Lee, Szabo, Fowler, and Wetsel have no financial discloses or conflicts of interest. Dr. Patkar is a Consultant for Gilead, Dey Pharma and Transtek Pharma; is on the Speaker's Bureau and received honoraria from Alkermes, Bristol-Myers Squibb, Dey Pharma, Merck, Sunovion and Pfizer, has received Grant Support from National Institutes of Health (NIDA, NIAAA), SAMHSA, AstraZeneca, Bristol-Myers Squibb, Cephalon, Forest, J & J, Jazz Pharmaceuticals, Lundbeck, Merck, Organon, Pfizer, Sunovion, Shire

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