A 'crash' course on psychostimulant withdrawal as a model of depression

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Most drugs of abuse generate diverse behavioral and neurochemical effects in mammals. However, one feature common to many such drugs is the phenomenon of the withdrawal syndrome that results from termination of drug administration. Early drug withdrawal, often referred to as the 'crash' phase in humans, is characterized by adverse psychological and/or somatic symptoms. Withdrawal from psychostimulant drugs precipitates a transient and primarily psychological condition that bears remarkable similarity to the symptoms of major depressive disorder in humans. Rodent paradigms of psychostimulant withdrawal faithfully model the human condition. Associated behavioral deficits in these animals can be reversed by treatments with antidepressant properties, suggesting that psychostimulant withdrawal might provide the basis for an animal model of depression. Current advances and limitations in the development of this model, together with recent evidence that psychostimulant withdrawal in rodents can be used to screen for novel, rapidly acting antidepressant treatments, are discussed.

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The class of drugs known as 'psychostimulants' includes a broad range of psychoactive compounds that cause elevated behavioral and cognitive activity. In humans, withdrawal from many of these compounds leads to effects that vary in nature and intensity, depending on the specific drug and dose. Certain drugs induce a withdrawal syndrome that is manifestly similar to the symptoms of major depressive disorder (MDD). This important property of these compounds provides the basis for an animal model of depression, which is reviewed in this article.

Frequently used psychostimulants that are legally available in most countries include caffeine and nicotine, whereas illicit psychostimulants include cocaine, amphetamine and substituted amphetamines, such as para-methoxyamphetamine (PMA) and 3,4-methylenedioxymethamphetamine (MDMA) [1]. Although abstinence symptoms have been widely reported after withdrawal from caffeine [2], these symptoms are rarely sufficient to require hospitalization. The psychological effects of nicotine withdrawal are more severe [3] and have been modeled effectively in animal paradigms [4]. However, nicotine abstinence differs from cocaine and amphetamine withdrawal in that it also is associated with numerous somatic symptoms not present in MDD and therefore will not be part of the focus of the present review.

Although the mechanism of action of cocaine and amphetamines is incompletely understood, both are known to alter the reuptake and release of monoamines by binding to plasmalemmal and vesicular monoamine transporters [5]. This property results in substantial increases in synaptic and extra-synaptic levels of dopamine, noradrenaline and 5-HT [6], which are generally assumed to underlie the euphorigenic effects of the drugs [7], although the relationship between the levels of these neurotransmitters and subjective mood is likely to be complex [8].

Psychostimulant withdrawal in humans

In general, both cocaine and amphetamines increase alertness, concentration and energy when taken in lower doses, whereas higher doses of these compounds produce additional euphorigenic effects that often are described as a 'high' or 'rush' [9]. These pleasurable effects decline rapidly, within minutes in the case of cocaine [10] or over a period of several hours in the case of D-amphetamine [11], depending partly on the route of self-administration. As the rewarding properties of the drug diminish, negative affective states emerge, which can be reversed by further administration of the psychostimulant drug. However, if the drug is not available, or if the individual chooses to terminate drug self-administration, the affective sequelae of withdrawal from the drug become apparent.

The psychological effects of drug withdrawal often have been explained within the theoretical framework of the opponent-process theory of motivation [12]. According to this theory, during withdrawal the previously pleasurable effects of drugs of abuse are followed inevitably by emotional states opposite in affect, and of a longer duration, as the body seeks to restore its 'hedonic equilibrium' [13] (Fig. 1). Thus, the acutely rewarding properties of psychostimulant drugs, which include euphoria, increased energy and self-confidence, generate a withdrawal syndrome characterized by anhedonia, lethargy and anxiety. In a seminal paper, Gawin and Kleber [14] described in detail the three-stage abstinence symptomatology of chronic cocaine users, in which early withdrawal (also known as the 'crash') was characterized by 'extreme dysphoria…full anhedonia…irritability, [and] a subjective sense of confusion', as well as 'temporary suicidal ideation' in 43% of the sample patient group. These effects gradually subsided to a milder dysphoria, anhedonia and anergia, with a full remission by 10 weeks. More recent studies of the effects of cocaine and amphetamine withdrawal [15–19] reported a similar constellation of abstinence symptoms, although support for the three-stage theory is generally weak because most patients' symptoms regress linearly over time and the duration of withdrawal effects is

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often substantially shorter than originally reported by Gawin and Kleber.

Psychostimulant withdrawal and 'depressive-like' symptoms

The features of psychostimulant withdrawal bear remarkable similarity to the symptoms of unipolar depression; indeed, the semblance can be so great that the clinician might have to differentiate between the two based solely on the suspected etiology of the condition [20]. A comparison of the effects of psychostimulant withdrawal with the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) diagnostic criteria for MDD, independent of symptom duration, shows that almost all of the indications of MDD are observed during psychostimulant withdrawal (Table 1). Similarly, strong evidence exists for many shared features of underlying physiology, including hormonal, electrophysiological and metabolic indices (Table 1). However, unlike MDD, most of these drug-induced effects are relatively transient in nature, whereas a hallmark of MDD is the persistence of its symptoms for months [20]. This latter issue raises questions about the degree to which MDD and psychostimulant withdrawal share a common etiology, and substantial further research is required to resolve this issue. Nevertheless, as described above, psychostimulant withdrawal is characterized by depressive symptoms that are observed in MDD. Thus, even if psychostimulant withdrawal might not be a model of the entire MDD syndrome, it allows the study of aspects of MDD.

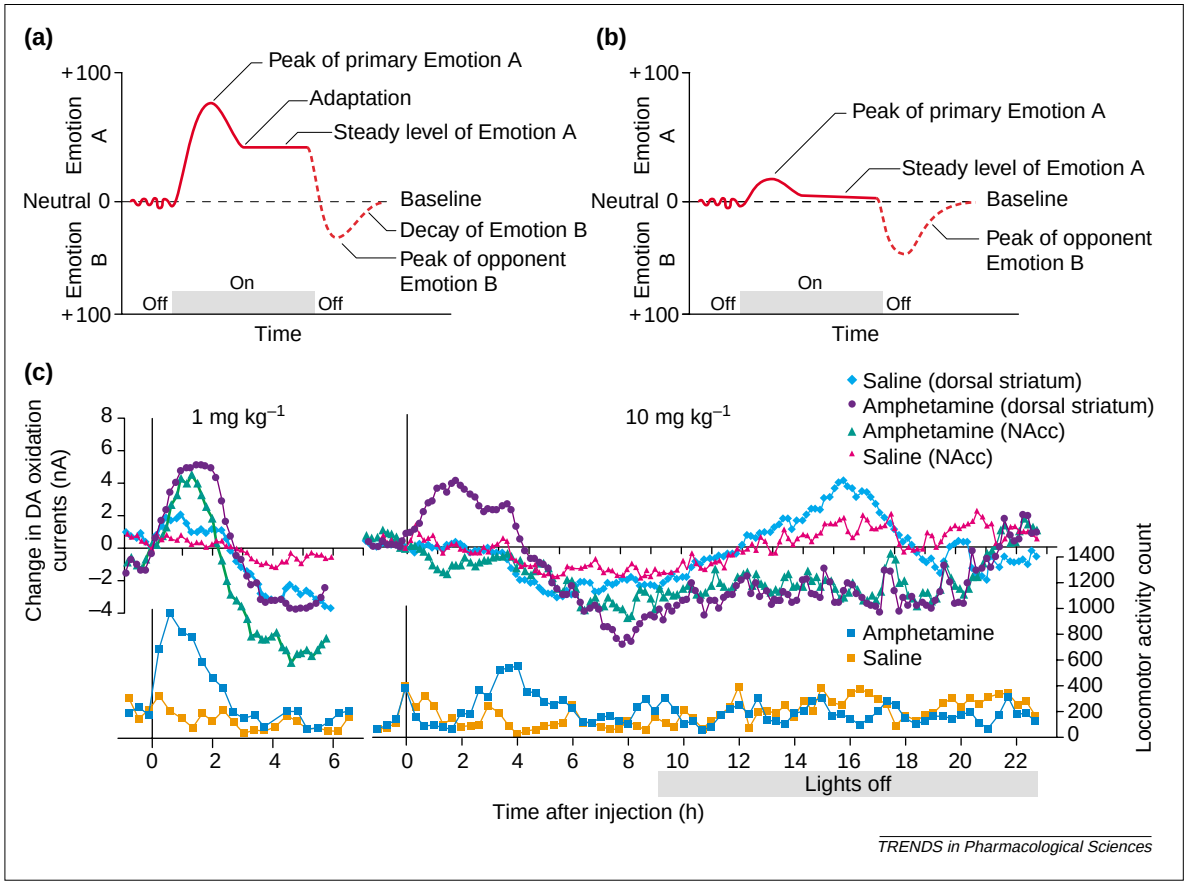

Fig. 1. (a) According to the opponent-process theory of motivation, as envisaged by Solomon and Corbit [13], emotions can be considered as pairs of opposites. Thus, when one emotion is experienced (Emotion A, off,on,off), an opposing emotion is triggered after a period of time (Emotion B). (b) With repeated stimulations, the opposing emotion increases in strength, decreasing the experience of the primary emotion and producing an enduring after-effect. (c) Support for this theory with respect to the initial effects of psychostimulant drugs and their withdrawal is shown. The acute indirect dopamine (DA) agonist property of D-amphetamine has been confirmed *in vivo*, using brain dialysis and electrochemical techniques, as a significant increase in DA efflux in both the dorsal and ventral striatum. Accordingly, it was of interest to examine whether adaptation in DA efflux occurs in response to an escalating dose schedule of D-amphetamine, used in conjunction with withdrawal, to induce symptoms of depression in rats. Chromoamperometry in combination with stearate-modified graphite paste electrodes, implanted into the dorsal and ventral striatum of individual rats, was employed to monitor changes in DA oxidation current throughout an escalating dose schedule of D-amphetamine (1–10 mg kg^{-1}) (similar to [34–37]) and for 24 h of withdrawal. As shown in the left panel, a 1 mg kg^{-1} dose caused a significant increase in oxidation current in both the dorsal striatum and the nucleus accumbens (NAcc; ventral striatum), followed by a decrease below pre-drug baseline values. All rats displayed a classic increase in locomotor activity counts in response to the drug. Adaptation to repeated administration of D-amphetamine is reflected in the absence of change in the chronoamperometric signal in the NAcc (ventral striatum) following administration of a dose of 10 mg kg^{-1}. A significant increase in DA efflux was observed in the dorsal striatum, along with a delayed increase in locomotor activity (right panel). Following the final dose of D-amphetamine the chronoamperometric signals in both the dorsal and NAcc (ventral striatum) declined significantly below baseline values for ~22 h. This pattern of change in DA oxidation current suggests a selective adaptation in the mesolimbic DA pathway that might be linked to the development of depressive symptoms following withdrawal from a 4-day escalating dose schedule of D-amphetamine. Data taken from [61].

Table 1. Similarities between major depressive disorder and psychostimulant withdrawal in humans[a]

Major depressive disorder	Psychostimulant withdrawal	Refs
Behavioral (DSM-IV criteria)		
Depressed mood and/or irritability	Severely depressed mood and/or irritability	[14]
Diminished interest or pleasure in daily activities	Loss of interest or pleasure in daily activities	[14]
Large increase or decrease in appetite	Increase in appetite	[17]
Insomnia or excessive sleepiness	Excessive sleepiness	[17]
Psychomotor agitation or retardation	Psychomotor retardation	[17]
Fatigue or loss of energy	Fatigue and/or loss of energy	[16]
Diminished ability to think or concentrate	Poor ability to concentrate or confusion	[14]
Feelings of worthlessness and/or guilt	Unknown	
Recurrent thoughts of death or suicide	Significant suicidal ideation	[14]
Behavioral (non-diagnostic)		
Feelings of restlessness	Restlessness	[14]
Comorbid anxiety	High levels of anxiety	[14]
Carbohydrate craving	Increased craving for carbohydrates	[19]
Elevated drug self-administration	Greater drug-seeking and drug-taking behaviors	[57]
Physiological		
Disturbed HPA axis	Increased HPA axis activity	[58]
Disrupted sleep architecture	Decreased REM latency; higher REM density	[59]
Changes in regional brain metabolism	Elevated metabolic activity in orbitofrontal cortex	[60]

[a]Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HPA, hypothalamic–pituitary–adrenal; REM, rapid eye movement.

At present, there is no reliable treatment that can reverse the effects of psychostimulant withdrawal rapidly and completely. The few effective treatments for psychostimulant withdrawal are drugs that act either directly or indirectly on monoamine systems, indicating pharmacological isomorphism with MDD. Thus, the list of drugs with recently reported beneficial properties includes amantadine, amineptine, venlafaxine and phentermine or fenfluramine [16–19], all of which increase synaptic levels of monoamines. It is important to note, however, that the interpretation of data from clinical human studies is often complicated by their bias in the selective recruitment of treatment seekers. In addition, subjects treated for psychostimulant withdrawal frequently co-present with depressive disorders, hence obscuring whether treatment is ameliorating the effects of drug withdrawal, or a pre-existing psychiatric condition.

Psychostimulant withdrawal as a model of depression

The similarity of psychostimulant withdrawal and depressive symptoms evident in MDD in humans provides the foundation for the development of an animal model of depressive symptomatology, in which valid comparisons can be made between the behavioral, physiological and pharmacological aspects of psychostimulant withdrawal in animals and humans. Rodents self-administer similar drugs of abuse as do humans [21]. Through the use of sophisticated behavioral paradigms, it has been shown that rodents also are subject to the aversive psychological and affective states associated with drug withdrawal. The remarkable similarity between the effects of psychostimulant withdrawal in rodents and symptoms of MDD in humans reflects the powerful 'face validity' of this model of depression [22–23], and for many symptoms, the solid construct validity of the model.

In general, animal models are designed to induce quantifiable behavioral alterations that parallel a specific symptom of MDD. Of the nine diagnostic symptoms that the DSM-IV [20] lists for MDD (Table 1), the majority can be modeled in rodent paradigms [22–23]. Although it is clear that those symptoms relying on self-report, including 'depressed mood' and 'suicidal ideation', cannot be modeled in rats, these symptoms are commonly described in humans experiencing psychostimulant withdrawal, and hence reflect a limitation of the species used for modeling, rather than an inherent weakness in the model itself. The remaining diagnostic criteria have been modeled to a greater or lesser degree in rodents. Changes in homeostatic behaviors, such as sleeping and eating, are readily measured in rats after withdrawal from psychostimulant drugs [24–25], whereas decreases in locomotor activity are also widely reported [26], and several recent studies have investigated the effects of psychostimulant withdrawal on cognitive processes [27]. Of note, the DSM-IV places special emphasis on two core symptoms for the diagnosis of depression, namely depressed mood and anhedonia, either one of which must be present for diagnosis. 'Depressed mood' relies partly on the self-report of subjective experience and therefore is difficult to confirm in rodents. Nevertheless, recent evidence suggests that psychostimulant withdrawal might be associated with a dysphoric state; for example, rats will develop a conditioned place aversion to an environment associated with withdrawal from cocaine [28]. Additionally, in a drug discrimination task, Stadler and co-workers [29] demonstrated that rats in amphetamine withdrawal selected a lever for which the pharmacological effects of a low dose of haloperidol had served as a discriminative stimulus. This form of stimulus generalization is consistent with the

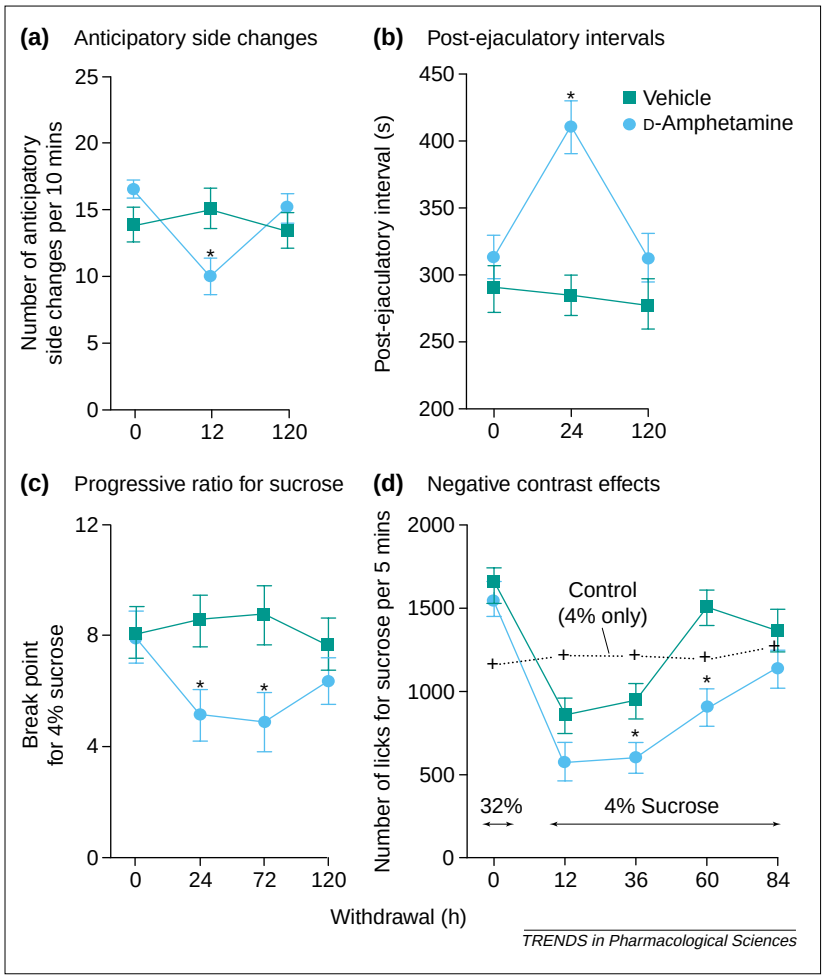

Fig. 2. A loss of pleasure or interest in normally rewarding activities is one of the core symptoms of depression, and can be readily modeled in rodents. Through the use of sophisticated behavioral paradigms, rats can be trained to respond for different natural rewards, which allows the unambiguous measurement of their motivation to obtain such stimuli. Sexual behavior was assessed in amphetamine-withdrawn male rats that were trained to anticipate exposure to a receptive female animal of the same species. Drug withdrawal was associated with (a) a decreased number of movements between opposite sides of the chamber normally displayed before presentation of the female (i.e. anticipatory side changes), and (b) increased post-ejaculatory intervals (the time taken from the previous ejaculation to reinitiate sexual behavior). (c) Rats were trained to respond on a lever for a 4% sucrose solution, under a progressive ratio schedule of reinforcement. According to the requirements of this schedule, rats must increase the number of lever presses for each subsequent reward, until a point is reached at which they fail to obtain the next reward within the time available. When rats were tested after withdrawal from a 4-day escalating dose schedule of D-amphetamine, they exhibited lower final ratios than control animals, indicating a substantial loss of motivation. (d) The discrete psychological effects of amphetamine withdrawal are also evident in the protracted recovery from exposure to a negative contrast paradigm in rats. Based on the unexpected devaluation in the reinforcing value of a sucrose solution (from 32% to 4%), withdrawn rats require significantly more time to return to control levels of consumption of the solution. These combined data indicate that the physical capacity of rodents to consume normally reinforcing stimuli remains unaffected by the withdrawal from high doses of psychostimulant drugs; rather, these animals exhibit reduced motivation to obtain such rewards, consistent with a specific loss of interest or pleasure in such rewards. *$P<0.05$ between groups. Data are modified, with permission, from [35–37].

hypothesis that the psychological and physiological consequences of psychostimulant withdrawal generalized to the dysphoria described after a low haloperidol dose in humans [30].

Anhedonia, the second core symptom of depression, which represents a 'markedly diminished interest or pleasure in all, or almost all, activities' [21] has proven to be more easily measured in rodent models of reward and depression than has depressed mood [23]. Owing to the relative ease of training rats to respond for reinforcing stimuli, manipulations that decrease the salience or 'rewarding' properties of these stimuli can be readily quantified in an objective and reliable manner. Most studies have examined the anhedonia associated with psychostimulant withdrawal by assessing animals responding for reinforcing electrical brain stimulation. Intracranial self-stimulation (ICSS) is a well-validated technique sharing many properties in common with natural reinforcers, and leads to neurochemical changes in brain areas, such as the nucleus accumbens (NAcc), in which reward processes are hypothesized to occur [31–32]. The use of ICSS allows experimenters to quantify the amount or frequency of current required to maintain responding by animals and hence provides a measure of the sensitivity of the reward system. Typically, psychostimulants reduce the current necessary to maintain threshold or half-maximal levels of responding, indicating that the reward system is stimulated. By contrast, during withdrawal from psychostimulant drugs, animals require higher intensity electrical brain stimulation to maintain responding, thereby verifying a deficit in reward function. Similar effects are observed with both amphetamines and cocaine, and the duration and magnitude of withdrawal are in proportion to the amount of drug consumed [33]; a comparable degree of anhedonia is evident in rats that self-administer [33] or receive passive injections of drug [34–37]. The effects of psychostimulant withdrawal typically range between two [34] to six days [38] duration, although some indices might be present for up to three weeks [39]. Natural rewards are also reduced in value during psychostimulant withdrawal (Fig. 2). We have recently shown that rats withdrawn from amphetamine display reduced motivation to obtain a sucrose solution under a progressive ratio schedule of reinforcement [35], exhibit decreased interest in a sexually receptive animal of the same species [36], and display a protracted recovery in a negative contrast paradigm [37]. These latter studies demonstrate clearly how psychostimulant withdrawal can produce discrete disturbances in psychological and affective processes, while leaving motor functions essentially unaffected, hence providing a model with better construct validity than several earlier models that were confounded by performance deficits [40].

Physiological effects of psychostimulant withdrawal

In addition to the behavioral similarities between psychostimulant withdrawal in rodents and symptoms of MDD in humans, there are also significant physiological parallels between the two situations. Numerous studies examining the neurochemical alterations associated with cocaine withdrawal, using *in vivo* techniques, have shown reduced extracellular levels of dopamine in limbic nuclei, such as the NAcc, during cocaine withdrawal [41], although equivocal findings in this region have been reported for

amphetamine withdrawal [42]. Because evidence indicates that unipolar depression is related to deficits in the mesolimbic dopamine system [7,43], these findings suggest a degree of etiological validity between the physiology of this model of depression and the human disorder. Similarly, the list of 5-HT-related deficits in MDD is extensive, including pre- and postsynaptic modifications, in addition to regional decreases in neurotransmission. Corresponding changes in pre- and postsynaptic 5-HT-mediated activity [44] have been observed during cocaine withdrawal in rodents, with decreased 5-HT-mediated neurotransmission in the NAcc [45]. To date, few studies have examined the role of noradrenaline during psychostimulant withdrawal [46] but, given the evidence for an important role for this catecholamine in MDD [47], further research is warranted.

Neuroendocrine modifications are another common physiological marker of MDD. Disruption of the hypothalamic–pituitary–adrenal (HPA) axis is prevalent, including elevated levels of cortisol, decreased dexamethasone-mediated negative feedback, and increased cerebrospinal levels of corticotropin-releasing factor (CRF) [48]. Studies indicated elevated levels of corticosterone 24 h after termination of a 'binge'-like dose of cocaine [49]. In agreement with the hypothesized role for CRF in depression, it also has been demonstrated that withdrawal from cocaine coincides with increased levels of CRF in limbic brain nuclei [50]. Future studies should seek to determine putative deficits in dexamethasone-mediated feedback because these represent one of the cardinal indicators of HPA axis dysfunction in depressive patients.

Pharmacological treatment of psychostimulant withdrawal

One of the primary purposes of animal models of depression, particularly for the pharmaceutical industry, is the identification of compounds with antidepressant properties. For a model to serve this function successfully, it must respond to drugs that exhibit antidepressant effects in humans, and hence display 'pharmacological validity' [22–23,40]. The model ideally should respond to all classes of compounds [such as tricyclic drugs, monoamine oxidase inhibitors and selective 5-HT reuptake inhibitors (SSRIs)] and false-positive compounds should be inactive, although this latter requirement is often complex; for example, the effects of amphetamine withdrawal can be rapidly reversed by re-administration of the drug, and although amphetamine is not generally prescribed for MDD, there is ample evidence that it has antidepressant properties [51].

In general, studies that have reported effects of treatment with different compounds on the behavioral symptoms of psychostimulant withdrawal in rodents provide the basis for an evaluation of the pharmacological validity of this model of depression (Fig. 3). In a recent landmark study, Harrison and colleagues [38] determined the capacity of the SSRI fluoxetine to attenuate the effects of amphetamine withdrawal on ICSS responding. The authors observed that fluoxetine shortened the effects of psychostimulant withdrawal, indicating a positive antidepressant response. Interestingly, co-administration of the relatively selective 5-HT_{1A} receptor antagonist p-MPPI {4-(2′-methoxy-phenyl)-1-[2′(*n*-(2′-pyridinyl)-*p*-iodobenzamido]-ethyl-piperazine} shortened the onset of therapeutic efficacy even further, implying that the psychostimulant withdrawal model of depression might be able to differentiate fast-acting antidepressant treatments from standard antidepressant treatments. There has been substantial interest in the 5-HT_{1A} receptor as a substrate for the development of rapidly acting antidepressants, and given the difficulty of detecting these putative compounds with conventional antidepressant screening paradigms, the findings of Harrison and colleagues indicate that the psychostimulant withdrawal model of depression might have unique potential in detecting fast onset-of-action antidepressant treatments [52]. This hypothesis is supported further by recent findings indicating that amphetamine withdrawal is mitigated after daily administration of electroconvulsive shock [34], whereas cocaine withdrawal is rapidly reversed by the adenosine A_2 receptor antagonist (a novel class of drugs with putative antidepressant properties [53]) 3,7-dimethyl-1-propargylxanthine (DMPX) [54].

Limitations of the model

Although recent advances in the development of the psychostimulant withdrawal model indicate substantial scientific potential for this paradigm, this model also has several inherent limitations. It should be noted that the transient nature of psychostimulant withdrawal in rodents, with effects typically observable for less than one week (and hence a narrow window for therapeutic intervention), might pose a theoretical challenge to the detection of novel antidepressant compounds because of the requisite 2–3-week period before therapeutic effects are noted in humans with most antidepressant treatments. However, this theoretical challenge has not hindered the practical development and use of alternative rodent models of antidepressant activity with high predictive validity, based on acute effects of these drugs [22,47]. Furthermore, rapid antidepressant effects of tricyclic drugs have been observed within 6 days in humans when administered at very high doses, such as by intravenous administration [55], possibly resembling more closely the active levels of drug administered to rodents.

Additionally, it should be noted that some behavioral effects of cocaine withdrawal are also responsive to anxiolytic drugs. Thus, drugs with anxiolytic properties, such as CRF antagonists, mitigate effects of cocaine withdrawal [56], but only in tasks that measure anxiety, such as defensive burying. It is unlikely, therefore, that these drugs would alleviate the anhedonic deficits measured in

paradigms such as ICSS responding, although this remains to be determined empirically.

An important practical limitation of the psychostimulant withdrawal model is its labor intensity; compared with other acute antidepressant screening paradigms such as the forced swim and tail suspension tests [22,52], substantial resources must be used to train animals to respond reliably in various tasks, before antidepressant effects can be detected with novel compounds. We suggest that because of the latter issue, the psychostimulant withdrawal model might be more useful as a secondary screen to detect selectively rapidly acting antidepressant compounds, following initial detection in simpler and faster screens.

Concluding remarks

The withdrawal from large doses of psychostimulant drugs in humans generates a syndrome with striking behavioral and physiological parallels to MDD. These effects have been modeled successfully in rodent paradigms, in which animals display reliable and highly reproducible behavioral and physiological alterations

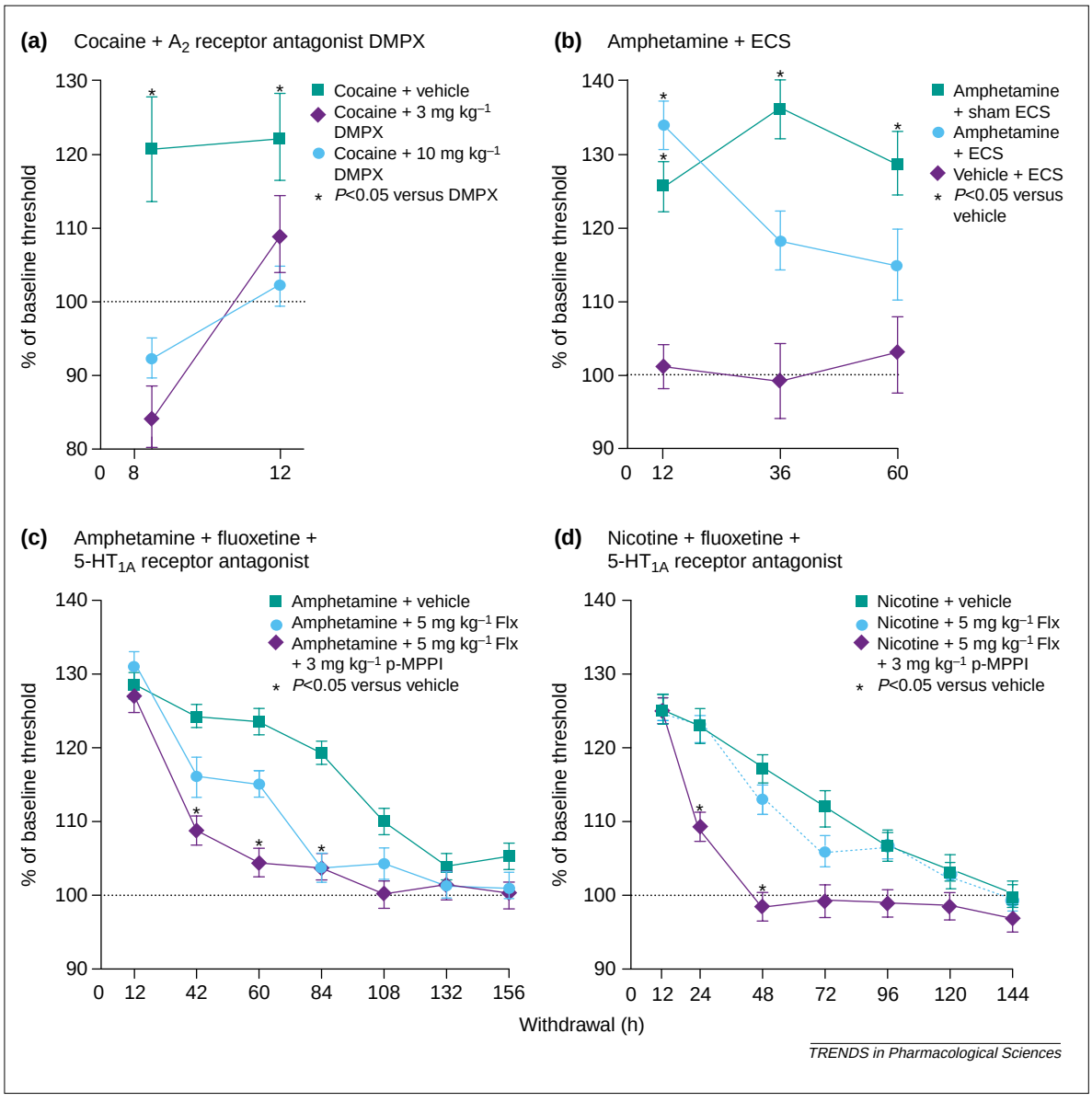

Fig. 3. The use of intracranial self-stimulation (ICSS) in rodents allows the precise measurement of changes in the responsiveness of the brain reward system. When responding for ICSS from electrodes located in the lateral hypothalamus, anhedonia can be inferred from elevated current intensities required to maintain threshold levels of responding. The effects of withdrawal from high doses of cocaine and amphetamines typically are manifest for up to six days following drug termination. During this period, pharmacological treatments can be used to ameliorate the effects of psychostimulant withdrawal. (a) Administration of the adenosine A_2 receptor antagonist 3,7-dimethyl-1-propargylxanthine (DMPX) completely reversed elevated reward thresholds at 8 h and 12 h following cocaine pretreatment. (b) Repeated exposure to daily electroconvulsive shocks (ECSs) for 3 days attenuated the anhedonia associated with withdrawal from a 4-day escalating dose schedule of D-amphetamine. (c) Pharmacological treatment with the selective 5-HT reuptake inhibitor antidepressant fluoxetine (Flx) reversed withdrawal-induced anhedonia, and this effect was accelerated and augmented by co-administration of the 5-HT_{1A} receptor antagonist p-MPPI {4-(2′-methoxy-phenyl)-1-[2′(*n*-(2′-pyridinyl)-*p*-iodobenzamido]-ethyl-piperazine}. (d) A similar cocktail was also effective in reversing the effects of nicotine withdrawal, further suggesting common neurobiological substrates mediating withdrawal from drugs of abuse and major depressive disorder. Data are modified, with permission, from [34,38,54].

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following withdrawal from both cocaine and amphetamines, although the effects on affective indices of withdrawal from other psychostimulants, such as MDMA, remain to be determined. Subtle motivational deficits can be measured objectively in animals that are trained to respond reliably for reinforcing stimuli, such as rewarding brain stimulation; many of these deficits can be reversed with standard antidepressant treatments, and it is particularly noteworthy that recent evidence suggests that this model might be useful in the detection of rapidly acting compounds. The high construct, face, etiological and predictive validities of the model also extend its utility beyond conventional drug detection, and the paradigm might represent an ideal candidate model for the application of contemporary multiarray genomic and proteomic technologies to investigate the neurobiological substrates of depression.

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Statins as anti-inflammatory agents

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The beneficial effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in cardiovascular disease have generally been attributed to their cholesterol-lowering property. However, an increasing number of *in vitro* and *in vivo* studies indicate that statins have direct anti-inflammatory effects that are not mediated by their hypocholesterolemic activity. In this article, the HMG-CoA-reductase-dependent and -independent mechanisms by which statins might affect leukocyte adhesion and migration to sites of inflammation are reviewed and the implications for the design of new statin-derived drugs are discussed.

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Statins represent a well-established class of drugs that effectively lower serum cholesterol levels and are widely prescribed for the treatment of hypercholesterolemia. They can be grouped into natural compounds such as lovastatin, simvastatin, pravastatin and mevastatin, and fully synthetic compounds such as fluvastatin and atorvastatin, which are marketed, and rosuvastatin and pitavastatin, which are in late-stage clinical development [1–3] (Fig. 1). Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the rate-limiting step of the cholesterol synthesis pathway in the liver and other tissues [2] (Fig. 2). By inhibiting HMG-CoA reductase, statins reduce cholesterol levels and might also lower intracellular levels of isoprenoids, such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate (Fig. 2). Isoprenoids are necessary for the post-translational lipid modification (prenylation) of a variety of proteins, thus anchoring them to the cell membrane [4]. Protein targets include the small guanosine triphosphate (GTP)-binding proteins that play a key role in signal transduction pathways that regulate cell proliferation, cell differentiation, vesicular transport and apoptosis [4].

In addition to their cholesterol-lowering activity statins have pleiotropic effects, including promotion of vasculogenesis [5,6], prevention of bone mass loss [7], and immunomodulatory [8] and anti-inflammatory effects. This review focuses on the anti-inflammatory properties of statins, with particular emphasis on their effects on the leukocyte adhesion cascade. The review is restricted to the effects of statins that are not considered to be a consequence of lowering cholesterol levels.

Clinical evidence for anti-inflammatory effects of statins

Clinical trials have demonstrated that statins reduce cardiovascular-related morbidity and mortality in patients with and without coronary artery disease and with or without elevated cholesterol levels [9–11]. Careful analyses of these trials indicate that statins might have effects that are not directly related to their cholesterol-lowering activity [12]. Thus, clinical benefits of statins manifest much earlier (within 1–2 years) than the effects of other cholesterol-lowering therapies, including ileal bypass surgery (>5 years), despite the fact that similar reductions in plasma cholesterol levels are achieved [12,13]. Furthermore, statins reduce the risk of stroke even though cholesterol levels are not considered to be a risk factor for stroke [14]. In heart-transplant recipients, statin therapy reduces the incidence of acute rejection episodes and coronary vasculopathy, and significantly

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