Does stimulant drug–induced sensitization occur in primates?

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Drug-induced sensitization is said to occur when a drug regimen leads to larger responses to the same dose or measurable responses to a previously ineffective low dose. Sensitization hypotheses of problematic substance use further propose that these effects facilitate the development of incentive responses to drug-paired cues.[1] These effects are well-established in rodents,[2–5] but, in some circles, it remains controversial whether they occur in primates (Box 1). What is the evidence?

Stimulant drug–induced behavioural sensitization in healthy humans

The first 2 attempts to demonstrate stimulant drug–induced behavioural sensitization in humans were unsuccessful.[42,43] Both administered low doses of *d*-amphetamine (5 or 10 mg, orally). In comparison, 80% of studies (8 of 10) administering at least 20 mg of *d*-amphetamine found evidence of sensitization.[44–51] Among the 6 studies that administered at least 3 doses of 20 mg or more, 100% found an effect.[44–47,49,50] The most consistent changes were to the drug's behaviourally energizing effects[12,13] with augmented responses continuing for at least a year[49] (Table 1).

Stimulant drug–induced behavioural sensitization in nonhuman primates

There is consistent evidence of cocaine and amphetamine-induced behavioural sensitization in nonhuman primates.[54–69] As in humans, augmented responses have been seen for psychomotor stimulation, but psychosis-like phenomena can emerge following high-dose regimens. The effects can last for more than 2 years[60] (Table 2).

Stimulant drug–induced behavioural sensitization in people with addictions

Clinical observations at least raise the possibility that people with stimulant drug addictions exhibit behavioural sensitization; e.g., markedly elevated incentive (drug-seeking) responses to small doses of the drug and drug-related cues. These observations noted, perhaps the most compelling demonstration that extensive substance use can lead to sensitization in humans investigated alcohol. In this 10-year prospective study, young adult drinkers (n = 163) received an alcohol challenge (0.8 g/kg, orally) at baseline and 5 and 10 years later.[38] Among those who developed an alcohol use disorder (AUD; n = 39), the self-reported alcohol-induced "wanting" and "stimulation" responses became progressively larger. The larger the wanting and stimulation responses, the greater the likelihood of developing an AUD and the greater the number of AUD symptoms.

Stimulant drug–induced dopamine sensitization in healthy humans

Based on studies in rodents, 2 neurotransmitters have been implicated in drug-induced sensitization: dopamine[2–4,70] and glutamate.[70–73] In humans, the transmitter release literature is both smaller and limited to dopamine, but evidence of amphetamine-induced sensitization has been found in all 3 studies that administered at least 3 doses (0.3–0.4 mg/kg, orally).[44,22,49] Correlational research suggests that these augmentations could continue to accumulate through to 150 uses or more.[20] The drug use histories that yield sensitization can also lead to conditioned dopamine release.[16,74]

Stimulant drug–induced dopamine sensitization in nonhuman primates

Two studies giving 10–50 stimulant drug exposures found sensitized dopamine responses in nonhuman primates;[75,76] 4 studies with more extensive regimens did not.[64,68,77,78] A number of explanations have been offered for the negative findings, including (1) small sample sizes (n = 4–6), particularly since, in both rodents and humans, only some develop an enlarged response;[13,49] (2) the absence of drug-related cues during testing, an important feature since the expression of sensitization can become context-dependent;[12,79,80] (3) the use of isoflurane,[81] an anesthetic that can alter dopamine cell firing and release; (4) evidence that drug-induced dopamine

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Box 1. Controversies

Contrary voices

Some well-respected researchers have expressed doubts that stimulant drug–induced sensitization develops in primates; e.g., "there is minimal evidence of sensitization in humans[6]," and "sensitization… does not appear to happen in primates.[7]" Curiously, the latter statement was made when commenting on a study that was not about sensitization. Rhesus monkeys had self-administered cocaine for 100 days but were tested without drug and in an environment that had been paired with the absence of drug.[8]

History of the controversy

The debate about sensitization in primates primarily reflects 2 related issues. First, questions remain about the mediating neurobiology following extensive drug use. Second, it has been suggested that the low dopamine responses seen in people with substance use disorders under some testing conditions are the primary driver of addiction-related behaviours.[9] In comparison, this writer and others propose that low dopamine states aggravate the clinical picture of addiction, but this does not include the ability to activate drug-seeking.[10–13] To the contrary, there is considerable evidence for the converse.[10,11,14] Dopamine release in humans is increased by all relapse triggers tested to date, including drug-related cues,[15–19] small quantities of the drug,[20,21] stress,[22,23] and, in people with long histories of opioid use, drug withdrawal.[24,25] As sagely noted by David Epstein,[26] no one feature is likely to account for all clinically relevant aspects of addiction. Claims that sensitization is not one of the critical elements are likely misguided.

Implications for clinical practice

The incentive sensitization model proposes that repeated, intermittent exposure to strong rewards progressively increases their ability to elicit approach.[4,12,13] These processes can become tied to either healthy or unhealthy pursuits.[13,27,28] There is little evidence that the effects can be reversed, but, among those with addictions, there is evidence that sensitization-influenced reinforcement processes can be redirected toward healthy ones; e.g., the financial rewards provided in contingency management therapy.[13,29]

The evidence of drug-induced sensitization in humans has also raised concerns about prescribing stimulant medications to youth with attention deficit/hyperactivity disorder. There is little evidence that standard continuous exposure regimens of low to moderate doses lead to sensitization, but problems might arise in some,[30] especially those who have been prescribed amphetamines as opposed to methylphenidate.[31] This requires further study.

Sensitization to nonstimulant drugs in primates

Few studies have tested whether "non-stimulant" drugs can produce sensitization in primates precluding confident conclusions. This noted, both alcohol and opioids can have stimulant effects and these effects can become sensitized in rodents.[32–34] In humans, there is preliminary evidence that striatal dopamine responses to alcohol[35,36] and alcohol-paired cues[37] are larger in high- than in low-risk drinkers, and alcohol use problems are associated with larger ethanol-induced stimulant responses[38] and striatal dopamine release.[39] Opioid sensitization in primates is less studied, and the relation to increased drug use remains less clear.[32] There is, however, some evidence that repeat morphine administration can lead to behavioural sensitization[40] and, in humans, early-life trauma is associated with increased risk of opioid use disorders and augmented morphine reward.[41]

sensitization is readily expressed following modest substance use[75] but not following the ingestion of greater quantities with only brief abstinence periods before testing;[77,82] (5) the possibility that, following many drug use sessions and the development of highly trained associations, dopamine cell reactivity comes to be influenced by reward-prediction errors (RPE; i.e., larger responses to unexpected drug delivery);[21] and (6) for cocaine, sensitized glutamate release might be more important than dopamine.[70]

Stimulant drug–induced dopamine sensitization in people with addictions

In people with addictions, there is some evidence of dopamine sensitization. Compared with healthy controls, people who used methamphetamine showed larger amphetamine-induced dopamine responses in extrastriatal regions.[83] Within the striatum, 1 study found larger responses to ethanol in people with an AUD[39] while another study[84] found larger responses to amphetamine in people with a gambling disorder. These studies noted, the most common finding in people with cocaine[85–88] and amphetamine use disorders[89] has been an absence of sensitized responses and even significantly reduced responses. These blunted responses may be specific to the testing conditions rather than evidence of ubiquitous dopamine deficits.[12,79,80,90] Indeed, there is well-replicated evidence that people with stimulant use disorders exhibit robust dopamine responses to drug-related cues.[15,17–19,91] Moreover, those with a cocaine use disorder can also exhibit larger stimulant drug–induced striatal dopamine responses than healthy volunteers when drug administration is unexpected.[21] Together, these findings indicate that, in this population, there remains only modest evidence of dopamine sensitization per se, but the potential for large dopamine responses is retained, differing only in when it is expressed.

Conclusion

This brief analysis yields 3 main conclusions. First, despite occasional claims to the contrary, there is overwhelming evidence of stimulant drug–induced behavioural sensitization in both human and nonhuman primates (18 of 19 studies administering at least 3 doses of at least 0.25 mg/kg of amphetamine or high-dose cocaine). Second, there is compelling evidence of dopamine sensitization in primates (5 of 5 studies administering 3–50 drug doses). Third, behavioural sensitization following extended high-dose drug use occurs, but more work is needed to understand the mediating neurobiology and when the augmented responses are expressed. Answering these questions will require thoughtful study designs. For laboratory research, this includes (1) testing awake subjects in the same environment where the drug was previously given, (2) administering the drug intermittently[92,93] with abstinence periods long enough to promote the incubation of both conditioned and sensitized responses, (3) testing how the influence of drug-paired cues (conditioning) and expectations (RPE) might change with progressively greater substance use, and (4) testing samples large enough to capture individual differences in susceptibility. Among those who are susceptible to drug use problems, features 1 and 2 resemble the early substance-use patterns that typically lead to a problem. This might not be a coincidence.

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Table 1: Stimulant drug–induced behavioural sensitization in humans

Study	No. of doses	*d*-Amphetamine regimen	Sensitization*
Johanson et al[42]	5	5.0 mg, p.o.	No — mood, no. of tablets chosen
Kelly et al[43]	6	10.0 mg, p.o.	No — speech rate, smoking, stimulant effects, liking
Kegeles et al[52]	2	~20 mg, i.v. (0.30 mg/kg)	No — euphoria, restless, anxiety
Wachtel et al[53]	2	20.0 mg, p.o.	No — subjective and psychomotor effects
Strakowski et al[46]	3	~20 mg, p.o. (0.25 mg/kg)	Yes — energy, eye-blink
Strakowski et al[47]	3	~20 mg, p.o. (0.25 mg/kg)	Yes — energy, euphoria
Strakowski et al[48]	2	~20 mg, p.o. (0.25 mg/kg)	Yes — energy, eye-blink, mood, speech rate
Boileau et al[49]	4–5	~20 mg, p.o. (0.30 mg/kg)	Yes — energy, eye-blink
O'Daly et al[50]	4	~20 mg, p.o. (0.30 mg/kg)	Yes — energy, euphoria
Childs et al[51]	2	20 mg, p.o.	No — stimulation, craving
Weidenauer et al[44]	4	~30 mg, p.o. (0.40 mg/kg)	Yes — lively, outgoing
Smart et al[45]	4	~20 mg, p.o. (0.30 mg/kg)	Yes — mind-racing, speech

i.v. = intravenous; p.o. = oral.
*There is consistent evidence of amphetamine-induced behavioural sensitization in humans administered a minimum of 3 doses ≥ 0.25 mg/kg (6 of 6 studies).[44–47,49,50]

Table 2: Stimulant drug–induced behavioural sensitization in nonhuman primates

Study	No. of doses	Stimulant regimen	Sensitization*
Tatum et al[54]	≤ 120	Cocaine, 5–30 mg/d, s.c. (1.67–10 mg/kg) for up to 4 mo	Yes — rhesus macaques (~3 kg) showed progressively greater excitement and susceptibilities to seizures.
Ellinwood[55]	≤ 111	Methamphetamine, 1–20 mg/d, i.m. 4–7 d/wk for 4–6 mo	Yes — rhesus monkeys showed progressively greater stereotypies that, with higher doses, became constricted and bizarre.
Garver et al[56]	12–46	*d*-Amphetamine, 2.0 mg/kg, n.g. twice daily for up to 3 wk followed by 3 wk abstinence	Yes — stumptail macaques developed increased activity, checking, stereotypies, harmful grooming and psychosis-like behaviours.
Post et al[57]	≤ 48	Cocaine, ≤ 16 mg/kg, i.p., twice daily	Yes — progressively increasing excitatory, stereotypic and psychosis-like behaviours.
Ellinwood et al[58]	≤ 180	Amphetamine, 1–25 mg/kg/d for 6 mo	Yes — progressively increasing, stereotypies and dyskinesias.
Ridley et al[59]	111	Amphetamine, 1–4 mg/kg, p.o. for 60 d Amphetamine plus haloperidol for 51 d	Yes — marmosets developed destructive grooming habits. The activating effects were reduced by haloperidol.
Post et al[61]	≤ 260	Cocaine, 10 – 17 mg/kg, i.p. twice daily 5 d/wk for up to 6 mo	Yes — rhesus monkeys showed progressively greater stereotypies, and increased susceptibilities to seizures, catalepsy, and abnormal visual tracking and staring.
Ridley et al[62]	35	*d*-amphetamine, 4–12 mg/kg/d, i.v.	Yes — vervet monkeys developed stereotypies followed by psychosis-like behaviours and over-responsiveness to stimuli.
Farfel et al[63]	56	Cocaine, 3.0–4.0 mg/kg, i.m. 4 times/d for 14 d	Yes — rhesus macaques developed stereotypies, visual tracking and splayed legs.
Castner et al[60]	120	S(+)-amphetamine, 0.1 mg/kg, i.m. escalating to 1.0 mg/kg, i.m. twice daily 5 d/wk for 12 wk Challenge doses (0.4–0.46 mg/kg, i.m.) were given following 6, 9, 12, and 28 mo abstinence	Yes — rhesus macaques developed increased pacing and stereotypies.
Castner et al[64]	60	*d*-amphetamine, 0.1–1.0 mg/kg, i.m. twice daily 5 d/wk for 6 wk	Yes — rhesus macaques developed increased fine-motor and oral stereotypies, parasitotic-like grooming, static posturing, etc.
Castner et al[65]	60	*d*-amphetamine, 0.1–1.0 mg/kg, i.v. twice daily 5 d/wk for 6 wk Challenge doses (0.4 mg/kg, i.v.) were given following 21 d and 6.5–8 mo abstinence	Yes — rhesus macaques developed increased fine-motor and oral stereotypies and hallucination-like behaviours.
Rodriguez et al[66]	660	Methylphenidate, 0.15–27 mg/kg, p.o. twice daily 5 d/wk for 66 wk	No change in rhesus monkeys on measures of executive function.
Gill et al[67]	365	Extended-release methylphenidate, ≥ 20 mg/d, p.o. for 12 mo	No change in the proportion of rhesus monkeys that acquired cocaine self-administration.
Soto et al[68]	182	Methylphenidate (12–16 mg/kg, p.o.) or *d,l*-amphetamine (0.7–0.8 mg/kg, p.o.) twice daily for 18 mo	No change in rhesus monkeys on measures of response speed or executive function.
Martelle et al[69]	365	Extended-release methylphenidate, ≥ 20 mg/d, p.o. for 12 mo	No change in methylphenidate self-administration.

i.m. = intramuscular; i.p. = intraperitoneal; i.v. = intravenous; n.g. = nasogastric; p.o. = oral; s.c. = subcutaneous.
*Contrary to the expectations of those writing the early papers, repeated stimulant drug administration did not lead to drug tolerance. As seen in laboratory rodents, lower doses produced behavioural hyperactivity while higher doses elicited stereotypies. With repeated administration, the behavioural responses became progressively greater and more disturbed, with higher doses eventually eliciting psychosis-like phenomenology, seizures, and dyskinesias. These effects were consistently observed for cocaine and amphetamines but not methylphenidate.

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