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Delayed emergence of methamphetamine's enhanced cardiovascular effects in nonhuman primates during protracted methamphetamine abstinence

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ABSTRACT

Background: Methamphetamine abuse is linked with brain abnormalities, but its peripheral effects constitute an integral aspect of long-term methamphetamine use.
Methods: Eight male rhesus monkeys with long histories of intravenous methamphetamine self-administration were evaluated 1 day, and 1, 4, 12, 26, and 52 weeks after their last methamphetamine self-administration session. On test days, isoflurane-anesthetized animals received a 0.35 mg/kg IV methamphetamine challenge. A control group consisted of 10 age and gender matched drug naïve monkeys. Cardiovascular responses to methamphetamine were followed for 2.5 h. Echocardiograms were acquired at 3 and 12 months of abstinence and in the control animals.
Results: No pre-methamphetamine baseline differences existed among 7 physiological measures across all conditions and controls. As expected, methamphetamine increased heart rate and blood pressure in controls. However, immediately following the self-administration period, the blood pressure response to methamphetamine challenge was reduced when compared to control monkeys. The peak and 150-min average heart rate increases, as well as peak blood pressure increases following methamphetamine were significantly elevated between weeks 12 to 26 of abstinence. These data indicate the development of tolerance followed by sensitization to methamphetamine cardiovascular effects. Echocardiography demonstrated decreased left ventricular ejection fraction and cardiac output at 3 months of abstinence. Importantly, both cardiovascular sensitization and cardiotoxicity appeared to be reversible as they returned toward control group levels after 1 year of abstinence.
Conclusions: Enhanced cardiovascular effects may occur after prolonged abstinence in addicts relapsing to methamphetamine and may underlie clinically reported acute cardiotoxic events.
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1. Introduction

Methamphetamine is an approved pharmacotherapy for attention deficit hyperactivity disorder (ADHD) and obesity, yet its clinical utility is limited due to high levels of abuse. Several methamphetamine epidemics have occurred since the first widespread abuse was reported during the post-World War II era, and its abuse remains problematic in Asia, Australia, and North America (Gawin and Ellinwood, 1988; Krasnova and Cadet, 2009; Lineberry and Bostwick, 2006; Seiden and Ricaurte, 1987; Ujike and Sato, 2004). As an abused stimulant, methamphetamine offers the promise of euphoria, feelings of being energized, positive mood, and enhanced sexual pleasure. These psychopharmacological actions are accompanied by stimulation of the cardiovascular system, principally elevating blood pressure and accelerating heart rate in humans (Kirkpatrick et al., 2012; Martin et al., 1971) and animals (Schindler et al., 1992; Varner et al., 2002). Such pressor and tachycardic effects can place the methamphetamine user at acute cardiotoxic risk (Kaye et al., 2007).

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Table 1
Intake histories for methamphetamine (METH) hydrochloride and age of rhesus monkeys in the self-administration (SA) cohort. Ages are rounded to the nearest half-year and SA length was rounded to the nearest month.

Subject	Age METH SA onset: years	Years METH SA	Maintenance dose: μg/kg/inj	Daily intake: mg/kg	Lifetime intake: mg
Sv	4	8.6	5	0.73	1760
Ch	3.5	3.8	5	0.40	404
Go	4	5.8	10	0.56	564
Gz	4	3.6	5	0.40	222
Ha	4.5	7.8	10	1.20	2454
Sc	3.5	3.8	10	0.82	748
Dj	4.5	5.9	10	0.54	521
Ji	4	4.7	10	0.70	710
Avg ± sem	4.0 ± 0.1	5.5 ± 0.7	9 ± 1	0.67 ± 0.08	751 ± 257
Range	3.5–4.5	3.6–8.6	5–10	0.40–1.20	404–2454

In the context of chronic methamphetamine use, the characteristic psychopathology includes psychosis, mood and anxiety disorders, and cognitive deficits (Darke et al., 2008). Limited preclinical evidence demonstrates enhanced chronotropic and pressor responses to methamphetamine in rodents following repeated dosing (Fukunaga et al., 1987; Varner et al., 2002; Yoshida et al., 1993), suggesting that sensitized processes may underlie the cardiac arrhythmias and sudden cardiac death in humans following re-exposure to methamphetamine, even after low doses (Kaye et al., 2007). However, tolerance to the cardiovascular effects of methamphetamine following chronic treatment also was reported (Perez-Reyes et al., 1991).

Less prominent is the available clinical evidence suggesting that the risk of cardiovascular complications can become chronic in nature, often persisting beyond the period of active methamphetamine use into the timeframe comprising acute and protracted abstinence. During these phases of abstinence the compounding of acute and long-term cardiotoxic effects can enhance the risk of cardiac pathology and includes fatal outcomes (Cruickshank and Dyer, 2009; Kaye et al., 2007). Abstinence from methamphetamine is formidable as the user may be confronted with depression, sleeplessness, anxiety, and fatigue, subjective effects that are in stark contrast to its initially pleasurable effects (London et al., 2004). Other obstacles to remaining abstinent include the psychological manifestations of drug craving, drug-conditioned cues, and stress (Sinha et al., 1999) leading to direct re-exposure to the drug (Jaffe et al., 1989).

We employed a longitudinal, within-subjects design not available in human studies to evaluate the cardiovascular consequences of long-term methamphetamine use and abstinence in a rhesus monkey self-administration model. Tolerance to methamphetamine's cardiovascular effects were assessed immediately following long-term methamphetamine drug exposure. Cardiovascular effects of methamphetamine were then assessed periodically throughout 1 year of abstinence in a cohort of rhesus monkeys who averaged 5.5 ± 0.7 years of intravenous methamphetamine self-administration. Dependent variables included heart rate, blood pressure, plasma methamphetamine concentrations, and intermittent echocardiograms. The efficacy of a methamphetamine challenge on the cardiovascular system during protracted abstinence revealed a dynamic cycle of tolerance, enhanced effects, and normalization that were not attributable to drug pharmacokinetic changes.

2. Methods

2.1. Subjects

This study was approved by the NIDA-IRP Animal Care and Use Committee. Rhesus macaques (*Macaca mulatta*) were individually housed and maintained on a standard diet of monkey biscuits, fresh fruit, and vegetables with water available *ad libitum*. Monkeys participated in a daily environmental enrichment program after their study sessions with continual visual, auditory, and olfactory contact with other cohorts. There were two cohorts of subjects: a methamphetamine self-administration group ($n = 8$) and a control group ($n = 10$). The groups were matched for age: controls, 10.6 ± 0.2 year (9 M, 1F) and methamphetamine-experienced population, 9.5 ± 0.8 year (8 M).

The self-administration group had 3.6 to 8.6 years (5.5 ± 0.7 year) of methamphetamine exposure (Table 1). During the self-administration studies, monkeys were anesthetized with ketamine (10 mg/kg IM) every other week to inspect the catheter exit site or check catheter patency. Catheters were replaced as necessary. In contrast, the drug-naïve controls were only exposed to pharmacological agents as part of their regular physical examinations. Details of the self-administration training and equipment can be found elsewhere (Schindler et al., 2011). Daily sessions included a 3-hr self-administration component during which the monkeys could self-administer up to 4 mg/kg methamphetamine. During the years that each monkey performed methamphetamine self-administration, test compounds were occasionally substituted for methamphetamine and various pharmacological pretreatments were given (see Schindler et al., 2010, 2011). Several test compounds, whose names cannot be revealed due to confidentiality agreements with pharmaceutical companies, were administered blind by investigators as potential therapeutics, and most were tested at multiple doses.

2.2. Study time frame

The experimental rhesus monkey group had extensive histories of methamphetamine self-administration, ranging from 3.6 to 8.6 years, and our goal was to evaluate this cohort during 1 year of abstinence with non-invasive MRI imaging techniques (Yang et al., 2015). Initiation of the study began within 24–28 h of the last session of methamphetamine self-administration (Day 1) and continued for 1 year. Following Day 1, experiments were performed at 1, 4, 12, 26, and 52 weeks after the final self-administration sessions. After 12 weeks of abstinence, 3 subjects were euthanized in order to harvest brain tissue. Consequently, at weeks 26 and 52, only 5 subjects comprised the methamphetamine group. Each animal in the drug-naïve control group was tested once with methamphetamine.

2.3. Experimental procedures

Animals were initially anesthetized with ketamine (10 mg/kg IM) and intubated, after which two venous lines were placed in the right and left saphenous veins. A continuous infusion of propofol (0.4–0.6 mg/kg/min) was started to maintain anesthesia while the animal was transported to the imaging suite at which time

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