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Behavioral and neurochemical effects of amphetamine analogs that release monoamines in the squirrel monkey

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ABSTRACT

To date, there are no effective pharmacotherapies for treating psychostimulant abuse. Previous preclinical and clinical studies have shown that continuous treatment with the monoamine releaser amphetamine reduces cocaine self-administration, but amphetamine selectively targets the dopamine system and is reinforcing. In the present study, we examined the consequences of administration of amphetamine and three structurally related analogs that vary in their potencies for releasing dopamine and serotonin on behavioral-stimulant effects and nucleus accumbens dopamine levels in squirrel monkeys. Amphetamine and PAL-353, which have relatively high selectivity for releasing dopamine vs. serotonin, increased accumbens dopamine levels and induced stimulant effects on behavior maintained by a fixed-interval schedule of reinforcement. PAL-313, which has a relatively low selectivity for releasing dopamine vs. serotonin, increased dopamine levels, but did not induce behavioral-stimulant effects. PAL-287, which is relatively nonselective in releasing dopamine and serotonin, did not increase dopamine levels or induce behavioral-stimulant effects. These results demonstrate that increasing serotonergic activity attenuates dopamine release and dopamine-mediated behavioral effects of monoamine releasers. In addition, these results support further investigation of PAL-313 and similar compounds as a potential medication for treating psychostimulant abuse.

1. Introduction

Psychostimulant abuse is a significant public health problem, with 2.1 million Americans reporting cocaine use and 1.9 million reporting methamphetamine use in 2006 (Substance Abuse and Mental Health Services Administration (SAMHSA), 2007). Unfortunately, there are no currently FDA-approved pharmacotherapies to treat stimulant dependence (Volkow and Li, 2004). Agonist substitution therapies have been successful in treating patients dependent on opioids (Kreek, 2000) or nicotine (Henningfield, 1995). Thus, drugs that have pharmacological and behavioral effects similar to those of psychostimulants have the potential to be effective medications for psychostimulant abuse. In order to identify these potential medications, there needs to be a better understanding of how psychostimulants produce their behavioral and neurochemical effects.

Psychostimulants interact with monoamine (dopamine, norepinephrine, and serotonin) neurons in the central nervous system. These neurons express specialized plasma membrane proteins that transport monoamines from the extracellular space back into the cytoplasm. Binding to these transporter proteins [dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT)] is the principal mechanism for inactivation of monoamine signaling (Howell and Kimmel, 2008). Drugs that interact with these transporters can be categorized as either reuptake inhibitors or substrate-type releasers, based on their mechanism of action. Reuptake inhibitors bind to transporters without being taken up into the cell. This binding blocks the reuptake of released neurotransmitter molecules, thereby elevating extracellular neurotransmitter levels in an impulse-dependent fashion. In contrast, substrate-type releasers bind to the transporter proteins and are then transported into the cytoplasm of nerve terminals. These releasers elevate extracellular neurotransmitter levels in two ways: by promoting efflux of the transmitter through the transporter protein and by increasing cytoplasmic transmitter levels by disrupting transmitter

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storage in vesicles (Rudnick, 1997; Rudnick and Clark, 1993; Sulzer et al., 2005).

Although cocaine is a nonselective inhibitor of all three monoamine transporters (Madras et al., 1989; Reith et al., 1986), the behavioral effects of cocaine associated with its abuse liability have been attributed primarily to its actions at DAT (Ritz et al., 1987). This has been substantiated in rodent, nonhuman primate, and clinical studies. A relationship between the potency of cocaine analogs at binding to the DAT in vitro and the potency of these analogs in vivo has been demonstrated by their locomotor-stimulant effects in rodents (Cline et al., 1992; Kuhar, 1993) and their cocaine-like behavioral effects in squirrel monkeys (Bergman et al., 1989; Madras et al., 1989; Spealman et al., 1989). The relevance of the DAT in the abuse liability of cocaine has been supported further by neuroimaging studies. In human cocaine users, a significant correlation was observed between the level of DAT occupancy and the magnitude of the subjective high following administration of cocaine (Volkow et al., 1997) or the behavioral-stimulant methylphenidate (Volkow et al., 1999). Similarly, the abuse-related behavioral effects of monoamine releasers, such as amphetamine and methamphetamine, have been attributed to their effects on dopamine (Hanson et al., 2004; Koob and Bloom, 1988; Wise, 1996; Wise and Bozarth, 1987).

The purpose of the present study was to investigate the neurochemical and behavioral effects of mixed-action monoamine releasers in squirrel monkeys. Amphetamine and three structurally related analogs (Fig. 1) were selected for comparison in these studies. While these drugs are equipotent in releasing dopamine in in vitro studies conducted in rodent tissue (Table 1), they vary in their potency for releasing serotonin. Within the group of selected compounds, amphetamine and PAL-353 are similar in their DA/5-HT releasing potency ratio, in that both are very selective for releasing dopamine. PAL-313 is less selective for dopamine, and PAL-287 even less so. The serotonin selective releaser fenfluramine was added to the behavioral studies for comparison. Our hypothesis was that, as the selectivity for serotonin release increased, drug-induced increases in extracelluar dopamine would decrease and drug-induced increases in locomotor activity would decrease accordingly.

Table 1
In vitro potency as releasers of monoamine neurotransmitters in rodent brain tissue.

Drug	EC_{50} (nM)		DA/5-HT
	[^{3}H]DA	[^{3}H]5-HT	
d-Amphetamine[a]	8.0	1756	0.004
PAL-353[a]	24.2	1937	0.01
PAL-313[a]	44.1	53.4	0.83
PAL-287[b]	12.6	3.4	3.7
Fenfluramine[b]	>10,000	79.3	126.1

Modified from [a]Wee et al., 2005 and [b]Rothman et al., 2007.

2. Methods

2.1. Subjects

Ten adult male squirrel monkeys (*Samiri sciureus*) weighing 700–1200 g served as subjects. Animals lived in individual home cages and had daily access to food (Harlan Teklad monkey chow; Harlan Teklad, Madison, WI; fresh fruit and vegetables) and unlimited access to water. All monkeys had prior exposure to cocaine and other drugs with selective dopaminergic or glutamatergic activity in various behavioral studies. Animal use procedures were in strict accordance with the National Institutes of Health "Guide for Care and Use of Laboratory Animals" (Publication no. 85-23, revised 1985) and were approved by the Institutional Animal Care and Use Committee of Emory University.

2.2. Apparatus

During daily behavioral test sessions, each of six animals was seated in a Plexiglas chair within a ventilated, sound-attenuating chamber (MED Associates, Georgia, VT). The chair was equipped with stimulus lights, a response lever, and a tail stock for delivering a mild electrical stimulus. Behavioral test sessions lasted approximately 90 min each day, 5 days/week. During microdialysis experiments in a separate group of four animals, the subjects were seated in a chair and fitted with an adjustable Lexan neckplate that was positioned perpendicular to the medial plane of the body just above the shoulder. These subjects had been acclimated to the chair and neckplate over several months prior to the start of these experiments. At least 2 weeks elapsed between the microdialysis experiments.

2.3. Guide cannulae implantation

A stereotaxic apparatus was used to implant CMA/11 guide cannulae (CMA/Microdialysis, Acton, MA) bilaterally to target the nucleus accumbens of the four monkeys in a procedure described previously (Czoty et al., 2000). Anesthesia was initiated with Telazol (tiletamine hydrochloride and zolazepam hydrochloride, 3.0 mg) and atropine. Inhaled isoflurane (1.0–2.0%) was administered to maintain depth of anesthesia during the procedure. A stainless steel stylet was placed in each guide cannulae when not in use. Analgesics [Banamine (flunixin

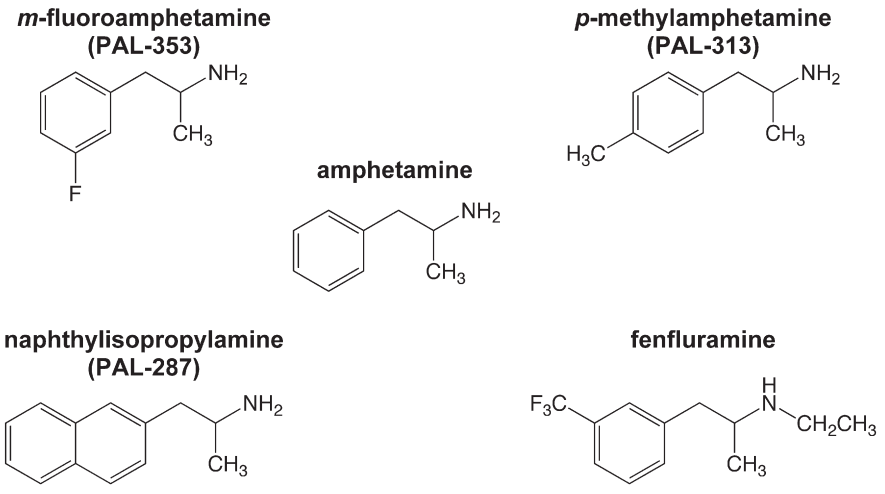

Fig. 1. Chemical structures of amphetamine and the four structurally related drugs used in these studies.