Review

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The Cognition-Enhancing Effects of Psychostimulants Involve Direct Action in the Prefrontal Cortex

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ABSTRACT

Psychostimulants are highly effective in the treatment of attention-deficit/hyperactivity disorder. The clinical efficacy of these drugs is strongly linked to their ability to improve cognition dependent on the prefrontal cortex (PFC) and extended frontostriatal circuit. The procognitive actions of psychostimulants are only associated with low doses. Surprisingly, despite nearly 80 years of clinical use, the neurobiology of the procognitive actions of psychostimulants has only recently been systematically investigated. Findings from this research unambiguously demonstrate that the cognition-enhancing effects of psychostimulants involve the preferential elevation of catecholamines in the PFC and the subsequent activation of norepinephrine α2 and dopamine D1 receptors. In contrast, while the striatum is a critical participant in PFC-dependent cognition, where examined, psychostimulant action within the striatum is not sufficient to enhance cognition. At doses that moderately exceed the clinical range, psychostimulants appear to improve PFC-dependent attentional processes at the expense of other PFC-dependent processes (e.g., working memory, response inhibition). This differential modulation of PFC-dependent processes across dose appears to be associated with the differential involvement of noradrenergic α2 versus α1 receptors. Collectively, this evidence indicates that at low, clinically relevant doses, psychostimulants are devoid of the behavioral and neurochemical actions that define this class of drugs and instead act largely as cognitive enhancers (improving PFC-dependent function). This information has potentially important clinical implications as well as relevance for public health policy regarding the widespread clinical use of psychostimulants and for the development of novel pharmacologic treatments for attention-deficit/hyperactivity disorder and other conditions associated with PFC dysregulation.

Keywords: ADHD, Cognition, Dopamine, Norepinephrine, Prefrontal cortex, Stimulants

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Psychostimulants elicit potent arousing, behaviorally activating, and reinforcing actions that are associated with significant potential for abuse (1–6). Nonetheless, these drugs are highly effective in treating hyperactivity, impulsivity, and inattention associated with attention-deficit/hyperactivity disorder (ADHD) (7–10). Given these apparently contradictory actions, it was initially proposed that psychostimulants acted paradoxically in individuals with ADHD: calming, rather than activating, behavior. This paradoxical hypothesis strongly influenced clinical and basic science research into the neurobiology and pharmacology of ADHD.

A major breakthrough in our understanding of psychostimulant action was the demonstration in 1980 that the cognition-enhancing and behavioral-calming actions of psychostimulants are not unique to ADHD, with similar effects seen in healthy human subjects (11). This and subsequent studies unambiguously demonstrated that when used at low and clinically relevant doses, psychostimulants improve prefrontal cortex (PFC)-dependent behavioral/cognitive processes in human subjects with and without ADHD (11–15). This ability of psychostimulants to act as cognitive enhancers drives the recent growth in use of these drugs by the general population to improve academic and work-related performance (16–18). Low-dose psychostimulant improvement in PFC-dependent function is consistent with evidence indicating ADHD involves dysregulation of the PFC and extended frontostriatal circuitry (19–22). Moreover, the procognitive actions of psychostimulants are also observed in normal animal subjects (5,6,23,24) (Figure 1), indicating an animal model of ADHD is not required to study the neural mechanisms underlying the cognition-enhancing/therapeutic effects of psychostimulants. This is an important advantage given there are no animal models known to definitively mimic the neurobiology of ADHD.

Collectively, these observations indicate that the neural mechanisms responsible for the therapeutic/cognition-enhancing effects of low-dose psychostimulants cannot be extrapolated from actions of higher doses that exert opposing behavioral and cognitive effects. Over the past 10 years, correlative evidence has suggested the hypothesis that the PFC is a key site in the cognition-enhancing actions of psychostimulants [for review, (25,26)]. More recent work provides critical, causal evidence for a role of the PFC in the cognition-enhancing effects of psychostimulants. In the

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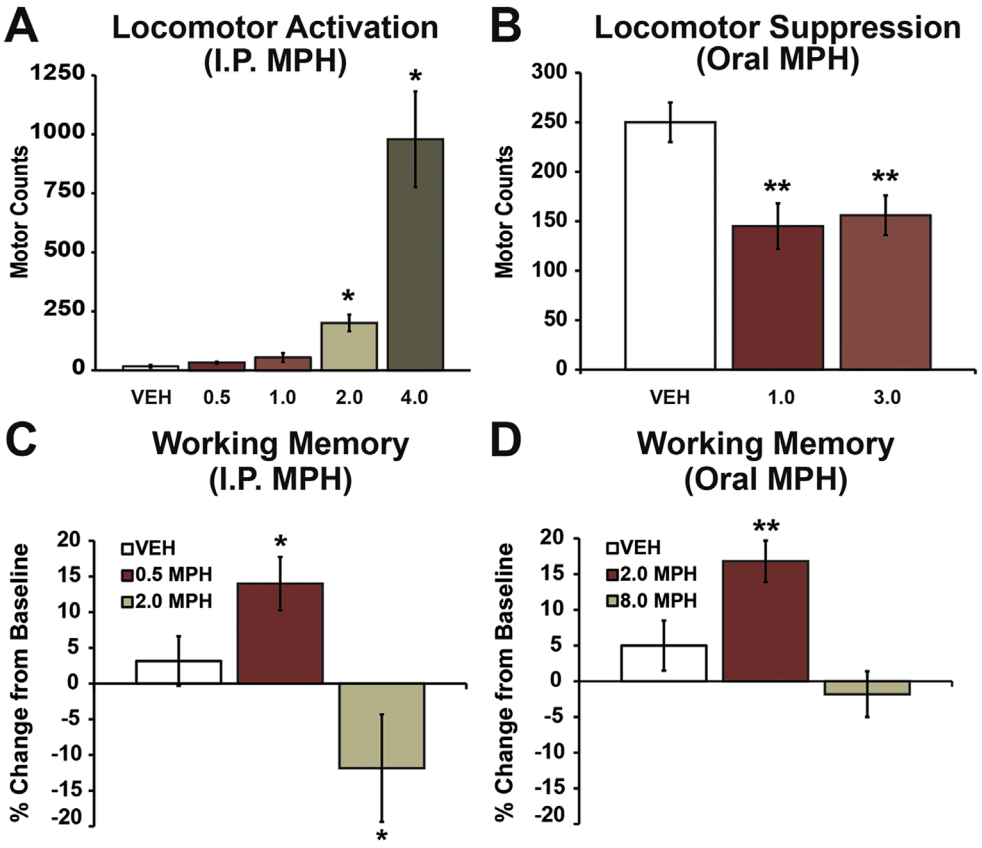

Figure 1. Behavioral-calming and cognition-enhancing actions of clinically relevant doses of methylphenidate (MPH) in rats. **(A)** Lack of locomotor activation. Bars indicate motor counts (quadrant entries + rears) in the 90-minute period following subcutaneous treatment with vehicle (VEH) or varying doses of MPH (.5, 1.0, 2.0, and 4.0 mg/kg) during the light (inactive) phase of the circadian cycle in rats (i.e., under low arousal conditions). Doses that produce clinically relevant plasma concentrations (.5, 1.0 mg/kg) do not elicit significant locomotor activation. Higher doses elicit dose-dependent increases in locomotor activity. The 4.0 mg/kg dose was perithreshold for eliciting mild stereotypy. **(B)** Motoric calming. When tested under conditions associated with elevated motor activity (during the dark/active phase), clinically relevant doses of oral MPH (1.0, 3.0 mg/kg) suppressed motor activity, similar to that seen in attention-deficit/hyperactivity disorder patients. **(C, D)** Cognition enhancement. When administered in doses that elicit clinically relevant plasma concentrations, .5 mg/kg intraperitoneally (I.P.) **(C)** or 2.0 mg/kg orally **(D)** administered MPH improves working memory performance as measured by percent change from baseline performance in a delayed-response test of working memory (T-maze). Fourfold higher doses impair or do not improve performance. All bars indicate mean ± SEM. $^{*}p < .05$, $^{**}p < .01$ compared with vehicle-treated animals. [Modified with permission from Devilbiss and Berridge (6), Berridge *et al.* (24), and Kuczenski and Segal (33).]

following sections, we review the collective body of research on the neurobiology of clinically relevant and procognitive doses of psychostimulants.

CLINICALLY RELEVANT DOSES OF PSYCHOSTIMULANTS ELEVATE CATECHOLAMINE SIGNALING PREFERENTIALLY IN THE PFC

The two most commonly used psychostimulants in the treatment of ADHD are methylphenidate (MPH) (e.g., Ritalin) and amphetamine (e.g., Adderall). At behaviorally activating doses, these drugs potently increase extracellular levels of norepinephrine (NE) and dopamine (DA) throughout the brain, largely by blocking NE and DA reuptake (27,28). Some psychostimulants, particularly amphetamine, actively stimulate DA efflux through the DA transporter (29). Although amphetamine can also stimulate NE efflux and block serotonin reuptake, these actions only occur at high and clinically inappropriate doses (30). In contrast, MPH acts only to block NE and DA reuptake, neither inhibiting serotonin reuptake nor stimulating NE or DA efflux (31).

Early animal studies demonstrated a central role of DA acting in the striatal subregion, the nucleus accumbens (NAcc), in the motor activating and reinforcing effects of higher doses of psychostimulants. Based on this, the early clinical literature emphasized the potential role of NAcc DA in the therapeutic effects of psychostimulants. However, given low, clinically relevant doses of psychostimulants exert qualitatively different behavioral effects versus higher, behaviorally activating doses, the neurobiology of higher doses may not have strong translational relevance. However, to study the clinically relevant actions of psychostimulants in animals, it is essential to identify doses that model clinical use. Pharmacokinetic studies identified doses of MPH in animals that elicit plasma concentrations associated with clinical efficacy in humans (~10–40 ng/mL) (23,24,32,33). In rats, clinically relevant plasma levels are seen following 1.0 to 3.0 mg/kg MPH given orally and .25 to 1.0 mg/kg MPH administered intraperitoneally (24,32,33). At these doses, MPH is largely devoid of behaviorally activating or arousing actions (24,32,33) (Figure 1). Moreover, under conditions associated with elevated locomotor activity, these clinically relevant doses of MPH suppress motor activity, similar to that seen in ADHD (33) (Figure 1). Finally, these doses of MPH improve PFC-dependent cognition (working memory, sustained attention), similar to that seen in humans (5,24,34) (Figure 1). The behavioral/cognitive effects of low and clinically relevant doses contrast with the motor-activating, arousal-promoting, and cognition-impairing actions associated with abuse-related doses of psychostimulants.