Psychostimulants as Cognitive Enhancers: The Prefrontal Cortex, Catecholamines and Attention Deficit Hyperactivity Disorder

Craig W. Berridge[*] and **David M. Devilbiss**
Department of Psychology, University of Wisconsin, Madison, WI

Abstract

Psychostimulants exert behavioral-calming and cognition-enhancing actions in the treatment of attention deficit hyperactivity disorder (ADHD). Contrary to early views, extensive research demonstrates that these actions are not unique to ADHD. Specifically, when administered at low and clinically-relevant doses, psychostimulants improve a variety of behavioral and cognitive processes dependent on the prefrontal cortex (PFC) in subjects with and without ADHD. Despite the longstanding clinical use of these drugs, the neural mechanisms underlying their cognition-enhancing/therapeutic actions have only recently begun to be examined. At behaviorally-activating doses, psychostimulants produce large and widespread increases in extracellular levels of brain catecholamines. In contrast, cognition-enhancing doses of psychostimulants exert regionally-restricted actions, elevating extracellular catecholamine levels and enhancing neuronal signal processing preferentially within the PFC. Additional evidence suggests a prominent role of PFC α_2- and D1 receptors in the behavioral and electrophysiological actions of low-dose psychostimulants. These and other observations indicate a pivotal role of PFC catecholamines in the cognition-enhancing and therapeutic actions of psychostimulants as well as other drugs used in the treatment of ADHD. This information may be particularly relevant for the development of novel pharmacological treatments for ADHD and other conditions associated with PFC dysregulation.

Psychostimulants are a class of drugs most commonly associated with potent arousing and behaviorally-activating actions as well as the significant potential for abuse (1–6). Nonetheless, these drugs, particularly methylphenidate and amphetamine, are widely used to calm behavior and improve cognitive function in children, adolescents and adults with attention deficit hyperactivity disorder (ADHD; 7–13). These seemingly contradictory actions of psychostimulants were initially thought to reflect unique and 'paradoxical' effects in individuals with ADHD. However, subsequent work unambiguously demonstrated that the cognition-enhancing and behavioral-calming actions of psychostimulants are not limited to ADHD. Thus, when administered at low and clinically-relevant doses, psychostimulants

[*]Correspondence: Craig Berridge, Ph.D., Department of Psychology, University of Wisconsin, 1202 W. Johnson St., Madison, WI 53706, Phone 608-265-5938, berridge@wisc.edu.

improve behavioral and cognitive processes dependent on the prefrontal cortex (PFC) in human subjects with and without ADHD (14–18). Moreover, these actions are not unique to humans, having been documented in 'normal' animal subjects when administered at clinically-relevant doses (i.e. doses that produce clinically-relevant plasma concentrations; see Figure 1;5,6,19–22). The cognitive/therapeutic actions of low-dose psychostimulants are observed acutely with neither pronounced tolerance nor sensitization associated with extended treatment (8,23; except see 19). The ability of low-dose psychostimulants to improve PFC-dependent function is consistent with evidence indicating ADHD is associated with a dysregulation of fronto-striatal circuitry (for review, 24–29).

Combined, these observations indicate that psychostimulants exert diverse behavioral and cognitive effects across a wide range of doses, with low and clinically-relevant doses facilitating PFC-dependent behavior/cognition. The cognition-enhancing actions of low-dose psychostimulants have been recently recognized by the general population, with rising use of these drugs on and off college campuses to improve academic and work-related performance by individuals without ADHD (30–32). Together, these observations indicate that an animal model of ADHD is not necessary to examine the neural mechanisms involved in the cognitive/therapeutic effects of low-dose stimulants. This is not a trivial advantage, given most animal models of psychopathology suffer from a high degree of uncertainty regarding the extent to which they model the neurobiology of a disorder, even when mimicking certain behavioral features of that disorder.

Neurochemical Actions of Low-Dose Psychostimulants: Preferential Targeting of PFC Catecholamines

Low and clinically-relevant doses of stimulants exert behavioral actions that are qualitatively different than higher and behaviorally-activating doses. At higher doses, psychostimulants block norepinephrine (NE) and dopamine (DA) reuptake, potently increasing extracellular levels of NE and DA widely throughout the brain (33,34). Some stimulants, particularly amphetamine, also actively stimulate DA efflux, an action believed to involve entry of the drug into DA terminals and a reversal in the operation of the DA transporter (35). Amphetamine can also stimulate NE efflux, though this only occurs at quite high, and clinically-inappropriate doses (36). Finally, amphetamine can also block serotonin reuptake, however, this too only occurs at relatively high and behaviorally-activating doses (34). In contrast to amphetamine, methylphenidate acts only to block NE and DA reuptake, neither inhibiting serotonin reuptake or stimulating NE or DA efflux (37).

Relative to higher doses of the psychostimulants, much less is known about the neurobiology of cognition-enhancing doses of psychostimulants. However, the neurochemical actions of psychostimulants reviewed above indicates that the cognition-enhancing actions of low-dose psychostimulants are not dependent on an ability of these drugs to block serotonin reuptake or actively stimulate catecholamine efflux. Moreover, recent microdialysis studies demonstrate that low and clinically-relevant doses of these drugs produce a preferential elevation in extracellular NE and DA within the PFC. Thus, in rats, doses of methylphenidate that elicit clinically-relevant plasma concentrations and improve PFC-dependent behavioral function (see Figure 1), produce prominent increases in extracellular levels of NE and DA within the PFC, while having substantially smaller effects on DA levels in the nucleus accumbens and NE levels in the medial septal area (see Figure 2; 20,21,38,39). This preferential targeting of PFC catecholamines is seen with both oral and intraperitoneally-administered methylphenidate, as long as dose is adjusted to yield similar plasma concentrations (21). Moreover, in both the hippocampus and somatosensory cortex, these same doses of methylphenidate elevate NE levels similar to that seen in the medial septal area and well below that observed in the PFC (20,38,39).

Collectively, these observations indicate an enhanced sensitivity of PFC catecholamines to cognition-enhancing doses of psychostimulants. This preferential sensitivity of PFC NE and DA to low-dose stimulants may involve low DA transporter (DAT) levels within the PFC combined with an ability of the NE transporter (NET) to clear extracellular NE and DA (40,41). Thus, due to competition between NE and DA for binding to the NET, increases in NE will result in less DA binding to the NET, resulting in an increase in extracellular DA levels. Conversely, increases in extracellular DA will result in greater competition for NE binding to the NET, resulting in an elevation in NE levels.

Do Psychostimulants Act within the PFC to Enhance Cognition?

The neurochemical effects of low-dose psychostimulants suggest the PFC may be an important site of action in the cognition-enhancing actions of these drugs. Consistent with this hypothesis, ongoing studies indicate that direct infusion of methylphenidate (0.5 μg/500 nl, but not 2.0 μg) into the dorsal anterior cingulate/dorsal prelimbic subfields of the medial PFC of rats improves spatial working memory performance, comparable to that seen with systemic administration (data not shown; Spencer and Berridge, unpublished observations). Though preliminary, these observations suggest that action within the PFC is sufficient for the cognition-enhancing actions of psychostimulants.

Although the PFC appears to be a principal site of action in the cognition-enhancing/ therapeutic effects low-dose psychostimulants, actions outside the PFC may well contribute to the behavioral/cognitive effects of these drugs. Indeed, the 25–50% increase in catecholamine levels observed outside the PFC with low-dose psychostimulant administration is likely physiologically- and behaviorally-significant. Given the posited role of frontostriatal circuits in both higher cognitive function and the pathophysiology of ADHD (42–46), increased DA neurotransmission in select striatal regions may well contribute to the behavioral effects of low-dose stimulants. PET imaging studies in humans indicate that clinically-relevant doses of methylphenidate result in DAT occupancy within the nucleus accumbens (47), consistent with results obtained in microdialysis studies (see above). Current sensitivity limits of PET do not permit imaging of DAT or NET occupancy in PFC or other cortical sites. However, the above-reviewed microdialysis studies suggest that clinically-relevant doses of methylphenidate will result in a greater occupancy of DATs and NETs in the PFC relative to the nucleus accumbens and other subcortical and cortical regions.

Although MPH may act outside the PFC to produce therapeutic/cognitive actions, the fact that low doses of stimulants produce only modest increases in NE/DA efflux in areas associated with stimulant-induced motor activation (e.g. accumbens; 48–51) and arousal (e.g. medial septum; 52,53) offers an explanation for why low doses of these drugs are devoid of behavioral-activating and arousal-enhancing effects typically associated with the psychostimulants. Moreover, the fact that low-dose stimulants exert only a modest impact on circuitry thought to underlie the abuse liability of these drugs (i.e. accumbens DA; 49,50) is consistent with evidence that indicates low-dose stimulants do not increase, and may reduce, the liability for drug abuse in ADHD populations (54,55).

Modulatory Actions of Low-Dose Psychostimulants on Noradrenergic Neuronal Discharge: Preservation of Phasic Discharge

The locus coeruleus (LC), provides the sole source of NE to the cortex and is implicated in a variety of behavioral and cognitive processes including attention, working memory, and decision making (for review, 17,56–58). LC neurons display both a spontaneous, or tonic mode of discharge, and an evoked, or phasic, mode of discharge. Tonic discharge rates are

causally related to arousal/wakefulness and the sensitivity of corticothalamic circuits to sensory signals (for review, 56,59). Phasic LC discharge is observed in response to behaviorally-relevant sensory stimuli, and is associated with decision/action (57) as well as sensory signal processing (60,61). Suppressive actions of low-dose stimulants on tonic LC discharge appear to be overcompensated by drug-induced elevations in extracellular NE (see Figure 2). However, given the role of phasic LC discharge in the regulation of behavioral actions, the behavioral/cognitive actions of low-dose stimulants could involve modulatory actions on phasic LC discharge patterns.

In anesthetized rats, high-dose stimulants profoundly suppress LC discharge via activation of somatodendritic α_2-receptors (62,63). In contrast, low and cognition-enhancing doses of methylphenidate only modestly suppress both tonic and phasic LC discharge in halothane-anesthetized rats (Figure 3;64). Importantly, at these lower doses, the signal-to-noise ratio for phasic vs. tonic LC discharge is largely unchanged (Figure 3). Phasic LC discharge is related to tonic discharge rates, with both low and high tonic discharge rates associated with weak phasic responses (for review, 56). Thus, it is important that in the halothane-anesthetized rat, spontaneous discharge rates of LC neurons are similar to those seen in quiet waking and LC neurons display robust phasic discharge to non-noxious sensory events (see 64).

The ability of low-dose stimulants to preserve the signal-to-noise ratio of phasic LC discharge suggests that any information conveyed by a phasic burst of action potentials superimposed on spontaneous discharge activity remains largely intact. Given the proposed role of phasic LC discharge in higher behavioral/cognitive function (57), the fact that low-dose stimulants *preserve* phasic LC signaling, as measured by the signal-to-noise ratio, is likely behaviorally significant. From this perspective, the therapeutic actions of low-dose psychostimulants may not stem directly from alterations in phasic LC discharge, but rather may involve the fact that they largely leave intact phasic LC signaling.

When considering the potential functional impact of psychostimulant-induced changes in LC discharge properties, a number of issues need to be considered. First, PFC-dependent neuronal and behavioral function can be facilitated by pharmacological manipulations directly within the PFC, such as intra-PFC infusions of NE/DA receptor agonists (see below). These manipulations result in the *sustained* activation of NE/DA receptors in the absence of direct actions on LC neurons. These observations indicate that sustained activation of PFC NE receptors is *sufficient* to facilitate PFC-dependent behavior.

Second, monoamine neurotransmission within the cortex appears to involve two distinct forms: synaptic transmission and extrasynaptic (or volume) neurotransmission. In the traditional view of synaptic transmission, quantal neurotransmitter release from a presynaptic terminal diffuses across a very short distance to receptors located within a specialized region of a post-synaptic neuron (post-synaptic specialization). This arrangement provides for a high-fidelity temporal coding of action potentials at the post-synaptic neuron. However, in addition to this type of 'synaptic' neurotransmission, anatomical evidence indicates that for NE and other monoamines, a large proportion of transmitter release sites are not in close proximity to post-synaptic specializations. In this case, the transmitter acts 'extrasynaptically', relatively distant to the release site (65). With increasing diffusion distance, the concentration associated with a bolus of neurotransmitter release decreases as the neurochemical signal becomes more spatially diffuse. Thus, extrasynaptic neurotransmission is not well-suited for the temporally-precise transmission of signals associated with a phasic burst of 2–3 closely spaced LC action potentials.

The microdialysis studies described above indicate that psychostimulants produce sustained and large elevation in basal NE levels in the PFC combined with smaller increases in NE outside the PFC. Thus, changes in NE levels driven by phasic LC discharge will be superimposed on drug-induced elevations in basal NE concentrations, the magnitude of which is regionally-dependent. In terms of extrasynaptic neurotransmission, it seems likely that relatively large psychostimulant-induced increases in extrasynaptic NE levels in the PFC will further dilute/mask phasic NE signaling associated with phasic LC discharge. Consistent with this, recent voltammetric studies within somatosensory cortex demonstrate that methylphenidate administration at a dose that produces relatively large increases in extracellular NE levels within this region (5.0 mg/kg) does NOT increase phasic NE signals and instead appears to decrease the amount of NE released per pulse (B.M. Willoughby, A. Khair, B.D. Waterhouse, K.A. Moxon, unpublished observations).

In terms of synaptic transmission (involving juxtaposed pre-synaptic and post-synaptic elements), it is possible that low-dose stimulants will comparably boost both basal NE (driven by tonic LC discharge) and phasic NE levels, leaving the ratio of these two measures unchanged. On the surface, this might be expected to maintain the functional impact of phasic discharge. However, extensive evidence demonstrates that NE exerts non-monotonic dose-dependent neuromodulatory actions (e.g. inverted-U shaped) the nature of which may be at least partially dependent on the activity state of the post-synaptic neuron (56,66,67). Thus, drug-induced elevations in *basal* NE (and DA) levels could shift the sensitivity of a neuron to phasic NE signals and the direction of this shift could be either upward or downward. Alternatively, electron microscopy studies suggest that the majority of membrane-bound DATs and NETs are not associated with traditional synaptic contacts (41,68). A sparsity of DAT/NET at the synapse would be expected to minimize the impact of DAT/NET blockade on the magnitude of phasic signals within the synaptic cleft (although, as reviewed above, tonic elevations in extracellular NE/DA may alter the responsivity of the postsynaptic neuron to these phasic signals).

There are a variety of models that have examined potential functional consequences of phasic and tonic LC discharge (69–71). However, for the purposes of the current discussion it is sufficient to note that none of these take into account: 1) the contributions of extrasynaptic vs. synaptic neurotransmission to the behavioral actions of tonic and phasic LC discharge; 2) the actions of low-dose psychostimulants on tonic/phasic LC discharge patterns that occur simultaneously with actions on tonic and phasic NE signaling across synaptic and extrasynaptic modes of neurotransmission, and; 3) the differential impact of low-dose stimulants on NE and DA levels/signaling across functionally-distinct catecholamine terminal fields (e.g. PFC vs. extra-PFC regions).

Modulatory Actions of Low-Dose Psychostimulants on PFC Neuronal Discharge: Facilitation of Signal Processing

Cognition-enhancing doses of psychostimulants produce relatively large increases in extracellular NE and DA in the PFC and modest alterations in spontaneous and evoked catecholamine neuronal discharge. For reasons outlined above, predicting the net influence of these actions on PFC neuronal function is difficult. To better understand how low-dose psychostimulants modulate PFC neuronal discharge properties, recent studies examined the effects of cognition-enhancing doses of methylphenidate on spontaneous and evoked discharge activity of PFC neurons in awake rats (6). In these studies, evoked discharge was elicited via electrical stimulation of the ventral hippocampus. This work indicates that cognition-enhancing doses of methylphenidate (0.5 mg/kg IP) increase the responsiveness of PFC neurons to afferent signals while exerting minimal effects on spontaneous discharge rates (Figure 4;6). Importantly, methylphenidate-induced increases in evoked responding are

observed for both excitatory and inhibitory responses. The ability of low-dose stimulants to enhance both excitatory and inhibitory afferent signals is consistent with the known neuromodulatory actions of catecholamines (56, see below).

Consistent with the regionally-limited neurochemical actions of low-dose methylphenidate described above (see Figure 2), this same dose of methylphenidate (0.5 mg/kg) does not alter neuronal discharge properties of cortical neurons outside the PFC (i.e. within the somatosensory cortex; 6). At modestly higher doses that fail to improve PFC-dependent cognition (2.0 mg/kg), methylphenidate no longer increases the responsiveness of PFC neurons but does alter somatosensory neuronal signal processing (39). In contrast to that seen with cognition-enhancing doses, high and behaviorally-activating doses of methylphenidate (15 mg/kg) produce a profound suppression of *evoked* discharge (~80%) along with a modest suppression of *spontaneous* discharge (~20%) of PFC neurons (Figure 4;6). Therefore, at the single neuron level, low-dose methylphenidate elicits a preferential and inverted-U shaped dose-dependent facilitation of evoked responding of PFC neurons. The nature of this inverted-U dose response curve largely parallels the dose-dependent actions of this drug on PFC-dependent behavior (Figure 1 vs. Figure 4).

Evidence indicates higher level behavior is dependent on the activity of large ensembles of neurons. Thus, ultimately, it is important that we understand the modulatory actions of low-dose stimulants at a neuronal ensemble level. Limited observations suggest that cognition-enhancing doses of psychostimulants modulate the activity of ensembles of PFC neurons in a manner that cannot be predicted solely from the actions observed at the single-neuron level. Specifically, in the electrophysiological studies described above, the discharge activity of multiple simultaneously recorded PFC neurons was analyzed using principal component (PC) analyses. These analyses demonstrated that cognition-enhancing doses of methylphenidate increase the dominant representation of afferent input to the PFC, as measured by the first principal component (PC1), while reducing higher dimensional patterns of distributed activity (PC2; 6). These neuronal ensemble-level actions also follow an inverted-U shaped dose-response curve similar to that seen at the single-neuron level. These observations provide proof-of-principle evidence that the cognition-enhancing actions of psychostimulants may involve alterations in neural coding embedded within the discharge activity of a population of PFC neurons.

Combined, these observations suggest that the cognitive/therapeutic effects of low-dose psychostimulants involve a facilitation of signal processing abilities of PFC neurons and PFC neuronal ensembles, potentially biasing neuronal responses to stronger and more salient information. In contrast, the cognition-impairing effects of high-dose stimulants likely involve a potent reduction in the signal processing abilities of PFC neurons. Consistent with these observations, imaging studies demonstrate that cognition-enhancing doses of stimulants increase task-related activity in the PFC of normal and ADHD subjects whereas cognition-impairing doses suppress activity within the PFC (16,72,73).

Non-Stimulant Cognitive Enhancers Used in ADHD Also Facilitate Catecholamine Neurotransmission Within the PFC

A number of drug classes has been demonstrated to be effective in the treatment of ADHD. These include selective NE reuptake inhibitors (both tricyclic antidepressants and non-tricyclic compounds), α_2-agonists, and monoamine oxidase inhibitors. A comparison of the neurobiological actions of these drugs with those of the psychostimulants provides important information for better understanding key neural/pharmacological mechanisms that contribute to the cognitive/therapeutic actions of ADHD-related treatments. This

information should prove useful in the development of new treatments for ADHD and/or or other conditions associated with PFC dysfunction.

1. Tricyclic Antidepressants and Selective NE Reuptake Inhibitors

Similar to the psychostimulants, tricyclic antidepressants are effective in the treatment of ADHD (74). As a class, these drugs block monoamine reuptake, particularly NE and serotonin (75). However, across the individual members of this class of drugs, there are differences in selectivity for the different monoamine transporters. For example, while imipramine displays high-affinity binding for both the serotonin and NE transporters, desipramine and nortriptyline, are highly selective for the NE transporter (76). Importantly, both desipramine and nortriptyline are effective in treating ADHD (77–81). Given selective serotonin reuptake inhibitors are ineffective in the treatment of ADHD (74), these observations suggest that the therapeutic actions of the tricyclic antidepressants involves their ability to block NE reuptake.

Tricyclic antidepressants also bind to and block a variety of receptors, including noradrenergic α_1-, cholinergic, and histaminergic receptors. However, these actions are typically viewed as contributing to the side effect profile of these drugs (e.g. anti-cholinergic, cardiovascular, sedative effects; 75,78,82). Consistent with this view, relative to the other tricyclic antidepressants, desipramine displays a lower affinity for many of these receptors and is associated with a reduced side effect profile but not decreased efficacy in the treatment of ADHD (74,77,78,83).

Atomoxetine is a non-tricyclic selective NE reuptake blocker. As with desipramine and nortriptyline, atomoxetine is effective in the treatment of ADHD (13,84,85). Unlike the tricyclic compounds, atomoxetine displays reduced affinity for neurotransmitter receptors and thus is largely devoid of tricyclic-like side effects (82,86). Similar to the psychostimulants, the cognitive/behavioral actions of atomoxetine are not limited to ADHD having been documented in 'normal' human and animal subjects (87,88).

Despite the selectivity of desipramine and atomoxetine for the NET (relative to other monoamine transporters), these compounds nonetheless increase extracellular levels of *both* NE and DA in the PFC, while having minimal effects on DA levels outside the PFC (at least in regions with low densities of NE fibers; 40,89). The ability of these selective NE reuptake blockers to increase both NE and DA levels in the PFC is posited to reflect the fact that the NET plays a prominent role in DA clearance in the PFC (see above, 40,90,91). However, given stimulants are typically described as more effective in the treatment of ADHD and stimulants block both NE and DA reuptake indicates that DA reuptake blockade and the consequent elevation of DA levels outside the PFC (though modestly) likely contribute to the therapeutic actions of psychostimulants.

2. α_2-Agonists

NE acts at three families of adrenergic receptors, α_1, α_2, and β receptors, each comprised of multiple subtypes. Across these families of NE receptors, α_2 receptors display a higher affinity for NE than α_1 and β receptors (92). Of particular relevance for the current discussion, there are three known subtypes of α_2-adrenoceptors: α_{2A}, α_{2B}, and α_{2C} (93). α_2-agonists have been well-documented to be efficacious in the treatment of ADHD (94, see below for further discussion). As with the psychostimulants and selective NE-reuptake inhibitors, these drugs improve PFC-dependent behavior in normal human and animal subjects (95–103). Early observations demonstrated that α_2 receptors are found pre-synaptically on NE terminals where they act as autoreceptors, reducing rates of NE neuronal discharge and NE release. The fact that α_2 agonists reduce extracellular NE levels while

stimulants and selective NE reuptake inhibitors have the opposite effect was initially difficult to reconcile. A significant advance in our understanding of noradrenergic function was the discovery that α_2-receptors are located both pre- and postsynaptically (93). Moreover, extensive evidence demonstrates that post-synaptic PFC α_2-receptors, particularly α_{2A}-receptors, promote PFC-dependent cognition, strengthen synaptic inputs to PFC neurons and enhance prefrontal network connectivity (104), all actions similar to those seen with low-dose psychostimulants (6, see elsewhere in this Special Issue). Thus, the available evidence suggests that the therapeutic and cognition-enhancing actions of α_2-agonists result from their ability to activation of post-synaptic α_{2A}-receptors (see below for further discussion).

3. Monoamine Oxidase Inhibitors

Though used less extensively than the other drug classes reviewed above, monoamine oxidase inhibitors have been demonstrated to be effective in the treatment of ADHD (74,105,106). By inhibiting the enzyme, monoamine oxidase, these drugs interfere with the degradation of NE, DA and serotonin, increasing catecholamine/monoamine neurotransmission. Low-dose deprenyl, a monoamine oxidase-B inhibitor, has been suggested to have a reduced impact on norepinephrine relative to DA and serotonin (75). Interestingly, low-dose deprenyl has been reported to be relatively ineffective in the treatment of ADHD (74,79,105,107). Though speculative, these observations suggest the efficacy of the monoamine oxidase inhibitors may be correlated with their ability to increase NE neurotransmission.

Early work demonstrated that amphetamine inhibits monoamine oxidase (for review, 35). Given the efficacy of monoamine oxidase inhibitors in ADHD, it was proposed that a common action of drugs effective for ADHD was an inhibition of monoamine oxidase (108). However, subsequent studies demonstrate that amphetamine-induced inhibition of monoamine oxidase occurs only at relatively high doses inappropriate for clinical use (for review, 35). Moreover, methylphenidate does not cross the cell membrane and thus cannot gain access to monoamine oxidase. Thus, the therapeutic actions of psychostimulants are unlikely to involve the inhibition of monoamine oxidase.

Behavioral and Electrophysiological Actions of Psychostimulants are Similar to the Modulatory Actions of Catecholamine in the PFC

As reviewed above, a large body of evidence strongly indicates an important role for PFC catecholamines in the cognition-enhancing/therapeutic actions of low-dose psychostimulants and other drugs used in the treatment of ADHD. The anatomical, neuromodulatory and behavioral actions of PFC catecholamines have been intensively studied for decades (see elsewhere in this Special Issue; 42,58,109). Although an in-depth review of this topic exceeds the scope of the current discussion, in this section we review evidence that suggests receptor mechanisms that likely contribute to the cognition-enhancing and therapeutic actions of psychostimulants and other ADHD-related drugs.

NE and DA brainstem nuclei extend efferents widely throughout the CNS (110). Consistent with their diffuse projection systems, catecholamines have been demonstrated to modulate a wide variety of behavioral and physiological processes via actions at a diversity of receptors (56). The PFC contains all major receptor families for both NE (see above) and DA, including D_1 (comprised of D_1 and D_5 receptors) and D2 (comprised of D_2, D_3, and D_4) receptor families (58,111). It should be noted that the D_4 receptor acts as a generalized catecholamine receptor, binding both NE and DA (112).

NE and DA exert an "inverted-U" shaped dose-dependent modulation of PFC-dependent function, with either too little (e.g. drowsy) or too much (e.g. stress) associated with an impairment in PFC-dependent function (113). The pharmacology of PFC-dependent behavior has been most extensively studied using delayed-response tasks of working memory (similar to those used to characterize the cognition-enhancing actions of low-dose psychostimulants reviewed above). Hallmark features of these tasks include the use of short delay intervals and a sensitivity to the debilitating effects of distractors and stress (see, 114). As reviewed above, stimulation of postsynaptic α_{2A} receptors in the PFC promotes performance in these tasks (for review, 113,115). In contrast, pharmacological stimulation of PFC α_1-receptors produces a stress-like impairment, while blockade of PFC α_1-receptors prevents stress-related impairment in performance in these tasks (113,116,117).

Based on these and other observations, it has been hypothesized that at lower rates of NE release higher affinity post-synaptic α_2 receptors are engaged, promoting PFC-dependent function, while at higher rates of NE release, associated with stress, lower affinity α_1-receptors contribute to stress-related impairment in PFC function (for review, 113). The differential activation of postsynaptic α_2 vs. α_1 receptors across varying rates of NE release results in an inverted-U shaped modulation of PFC-dependent behavior. Limited evidence suggests opposing actions of PFC β1 and β2 receptors on PFC-dependent behavior, with β1 receptors associated with impairment and β2 receptors associated with modest improvements in delayed-response tasks of working memory (118,119). The net contribution of these opposing actions of β1 and β2 receptors to psychostimulant-induced alterations in PFC-dependent behavior is unclear. In the case of DA, the inverted-U shaped modulation of PFC-dependent behavior involves, in part, inverted-U shaped actions of D1 receptors, with both low and high rates of D1 receptor stimulation associated with impaired PFC function (113,120).

One of the most intensively studied aspects of PFC neurophysiology is the sustained discharge displayed by a subset (approximately 30%) of PFC neurons during the delay-portion of delayed-response tasks (121). In the dorsolateral PFC of monkeys, delay-related discharge displays spatial tuning, with largest delay-related neuronal responses observed to stimuli within a restricted spatial location (122). Anatomically, α_{2A} and D_1 receptors appear to be located on separate dendritic spines on PFC pyramidal cells. This anatomical segregation of receptors offers the potential for these two receptor subtypes to differentially modulate qualitatively distinct afferent signals that arise from distinct neuronal populations (104,123). Indeed, electrophysiological evidence indicates that α_{2A} receptor stimulation strengthens behaviorally appropriate inputs, strengthening delay-related discharge for stimuli in the preferred spatial location, while D1 receptor stimulation weakens inappropriate inputs, reducing delay-related discharge to stimuli located in non-preferred spatial locations (113,120). Combined, these actions improve the spatial tuning properties of PFC neurons. In contrast, α_1-receptor stimulation or high rates of D1 receptor stimulation produce a general suppression of PFC neuronal activity, reducing spatial tuning properties (104,117).

Not all PFC-dependent tasks are impaired by PFC α_1-receptor activation. Specifically, in rodents extra-dimensional attentional set-shifting is facilitated by intra-PFC infusion of α_1-receptor agonists (124). Nonetheless, α_{2A}-agonists are used in the treatment of ADHD and these drugs improve performance in delayed alternation tasks but not in attentional set-shifting tasks (124). Thus, there is a close alignment between the pharmacology of the cognition-enhancing and therapeutic actions of drugs used in the treatment of ADHD and the pharmacology of delayed-alternation tasks of working memory, but not attentional set-shifting. Combined, these observations suggest that in terms of preclinical studies focused

on the pharmacology of ADHD, delayed-alternation tasks of working memory appear a more appropriate behavioral assay than attentional set-shifting tasks.

Cognition-Enhancing Actions of Low-Dose Stimulants Involve NE α_2 and DA D1 receptors

The available evidence suggests the cognition-enhancing actions of low-dose psychostimulants involve drug-induced increases in signaling at PFC α_2 and/or D1 receptors. Consistent with this hypothesis, the ability of low-dose methylphenidate to improve PFC-dependent behavior, as measured in delayed-response tasks, is prevented by systemically administered α_2 and D1 antagonists (at doses that have no impact on baseline cognitive function; 5). These observations suggest that the cognition-enhancing effects of low-dose psychostimulants are dependent on *both* α_2 and D1 receptors located within the PFC.

Moreover, preliminary data indicate that NE α_2 and DA D1 receptor antagonists prevent atomoxetine-induced improvement in PFC-dependent behavior (AFT Arnsten, unpublished observations), similar to that seen with the psychostimulants. Interestingly, although mianserin, a tetracyclic antidepressant, acts as a selective NE reuptake inhibitor (relative to other monoamines), this compound is not effective in treating ADHD (125). An important difference between mianserin and other selective NE reuptake inhibitors used to treat ADHD (desipramine, nortriptyline, atomoxetine), is that mianserin acts as a relatively high affinity α_2-antagonist and thus will block postsynaptic α_{2A} receptors (75). Combined, the available evidence indicates that the therapeutic/behavioral actions of low-dose stimulants and selective NE-reuptake blockers involve increased signaling at NE α_2 and DA D1 receptors in the PFC.

Do Psychostimulants Target the Underlying Etiology of ADHD?

The above-reviewed information suggests a prominent role of NE and DA in the pharmacology of ADHD. This is often interpreted as suggesting a role for NE and/or DA in the etiology of this disorder. However, it is important to note that treatments can be therapeutic while not targeting the biological origins of a disorder. As reviewed above, catecholamines act as neuromodulators, modifying the sensitivity of neurons to afferent signals. Available evidence suggests that the therapeutic actions of low-dose stimulants and other cognitive enhancers used to treat ADHD involve drug-induced modulation of modestly dysregulated PFC neuronal circuits via actions of PFC catecholamine receptors. Theoretically, this action could occur even if PFC dysregulation arises from mechanisms independent of catecholamine signaling. For example, if ADHD is associated with a dysregulation in PFC network connections, due to impaired development or other mechanisms, PFC α_{2A} and D1 receptors may well continue to facilitate PFC neuronal signal processing and PFC-dependent behavior. Given this, the fact that stimulants are effective in the treatment of ADHD does not necessarily indicate that ADHD involves dysfunctional catecholamine signaling.

Nonetheless, given ADHD is highly heritable and pharmacological treatments for ADHD enhance catecholamine neurotransmission, there has been substantial interest in the degree to which catecholamine-related genes may contribute to this disorder. Numerous studies have identified multiple catecholamine-related gene alleles that are associated with ADHD, including NE and DA receptors, DA and NE transporters and the NE synthetic enzyme, dopamine β-hydroxylase (126–128). Genetic insults to dopamine beta hydroxylase are of interest, as they reduce NE production and have been associated with weaker sustained attention, impaired PFC executive function, and increased impulsivity (129,130).

Despite these statistically significant genetic associations with ADHD, it is important to note that, in general, the variance in this disorder explained by any one of these genes is extremely small, often explaining no more than a few percent of variance (see 131). Additionally, evidence suggests that at least some of these genes may function as modifier genes, modifying rather than driving the behavioral phenotype of ADHD (see 132). Although these considerations do not rule out an involvement of catecholamine-related genes in ADHD, they suggest that, individually, the majority of these genes are unlikely to play a major role in the etiology of ADHD.

Synthesis and Future Directions

Low-dose psychostimulants facilitate a variety of behavioral and cognitive processes dependent on the PFC. These behavioral/cognitive actions are in stark contrast to the behaviorally-activating and cognition-impairing effects of higher doses of these drugs. Importantly, the cognition-enhancing and behavioral-calming properties of low-dose psychostimulants are not limited to ADHD: these drugs exert similar actions in both normal human and animal subjects.

Research over the past ten years has provided significant insight into the neurobiological mechanisms that support the cognition-enhancing and therapeutic actions of low-dose psychostimulants. This work indicates that cognition-enhancing doses of psychostimulants preferentially increase extracellular levels of catecholamines in the PFC while preserving phasic signaling of catecholamine neurons. The regionally-selective neurochemical actions of low-dose psychostimulants are in distinct contrast to the widespread actions of higher and behaviorally-activating doses of these drugs. At clinically-relevant doses, psychostimulants also exert a regionally-specific enhancement of neuronal responding to afferent signals within the PFC. This regionally-specific facilitatory effect on PFC neuronal signal processing contrasts with the more widespread electrophysiological actions seen with moderately higher doses as well as the profound suppression of PFC neuronal signaling seen with high-dose psychostimulants. These observations suggest a prominent role of PFC catecholamines in the behavioral/therapeutic actions of low-dose psychostimulants. Consistent with this, preliminary observations suggest intra-PFC infusion of low-dose psychostimulants facilitate PFC-dependent behavior similar to that seen with systemic administration.

Considerable evidence indicates that the cognition-enhancing/therapeutic actions of low-dose psychostimulants and other drugs used to treat ADHD are dependent on D1 and/or α_2 receptors within the PFC. This includes the similarity between the behavioral and electrophysiological actions of low-dose stimulants and the behavioral and electrophysiological actions of postsynaptic PFC α_2 and D1 receptors. Moreover, the cognitive/behavioral effects of low-dose stimulants are blocked by systemically administered α_2 and D1 antagonists. Although there has been a tendency in the literature to emphasize the potential role of DA in the therapeutic actions of low-dose stimulants, DA is neither the primary target of these drugs, nor the sole participant in their cognitive/behavioral actions. Combined, the available evidence strongly indicates that the cognition-enhancing/therapeutic actions of low-dose psychostimulants involve *both* NE and DA acting at postsynaptic α_2 and D1 receptors in the PFC.

There is substantial similarity between the behavioral and neurobiological actions of low-dose psychostimulants and other major classes of drugs used in the treatment of ADHD. This includes the ability of, psychostimulants, selective NE reuptake inhibitors (desipramine and atomoxetine) and α_2 agonists to improve PFC-dependent function in ADHD patients as well as normal human and animal subjects. Additionally, as with the psychostimulants,

selective NE reuptake inhibitors elevate *both* NE and DA in the PFC. Finally, for all major classes of drugs used in the treatment of ADHD, the behavioral/cognitive effects of these drugs are dependent on D1 and/or α_2 receptors.

Despite the hypothesized role of the PFC in the therapeutic actions of ADHD, drug actions outside the PFC may nonetheless be important for maximal therapeutic/cognitive benefit. A better understanding of the neurocircuitry involved in the cognitive/therapeutic effects of psychostimulants and other drugs used in the treatment of ADHD is an important issue for future studies.

Acknowledgments

References

1. Segal DS. Behavioral and neurochemical correlates of repeated d-amphetamine administration. Adv Biochem Psychopharmacol. 1975; 13:247–262. [PubMed: 1171583]

2. Rebec GV, Bashore TR. Critical issues in assessing the behavioral effects of amphetamine. Neurosci Biobehav Rev. 1984; 8:153–159. [PubMed: 6145135]

3. McGaughy J, Sarter M. Behavioral vigilance in rats: task validation and effects of age, amphetamine, and benzodiazepine receptor ligands. Psychopharmacology (Berl). 1995; 117:340–357. [PubMed: 7770610]

4. Berridge CW, Stalnaker TA. Relationship between low-dose amphetamine-induced arousal and extracellular norepinephrine and dopamine levels within prefrontal cortex. Synapse. 2002; 46:140–149. [PubMed: 12325041]

5. Arnsten AFT, Dudley AG. Methylphenidate improves prefrontal cortical cognitive function through alpha2 adrenoceptor and dopamine D1 receptor actions: Relevance to therapeutic effects in Attention Deficit Hyperactivity Disorder. Behav Brain Funct. 2005; 1:2. [PubMed: 15916700]

6. Devilbiss DM, Berridge CW. Cognition-enhancing doses of methylphenidate preferentially increase prefrontal cortex neuronal responsiveness. Biol Psychiatry. 2008; 64:626–635. [PubMed: 18585681]

7. Bradley C. The Behavior of Children Receiving Benzadrine. Am J Psychiatry. 1937; 94:577–585.

8. Greenhill, LL. Clinical effects of stimulant medication in ADHD. In: Solanto, MV.; Arnsten, AFT.; Castellanos, FX., editors. Stimulant Drugs and ADHD: Basic and Clinical Neuroscience. Oxford University Press; New York: 2001. p. 31-71.

9. Hechtman L, Abikoff H, Klein RG, Weiss G, Respitz C, Kouri J, Blum C, Greenfield B, Etcovitch J, Fleiss K, Pollack S. Academic achievement and emotional status of children with ADHD treated with long-term methylphenidate and multimodal psychosocial treatment. J Am Acad Child Adolesc Psychiatry. 2004; 43:812–819. [PubMed: 15213582]

10. Scheffler RM, Brown TT, Fulton BD, Hinshaw SP, Levine P, Stone S. Positive association between attention-deficit/hyperactivity disorder medication use and academic achievement during elementary school. Pediatrics. 2009; 123:1273–1279. [PubMed: 19403491]

11. Wender PH, Reimherr FW, Wood DR. Stimulant therapy of 'adult hyperactivity'. Arch Gen Psychiatry. 1985; 42:840. [PubMed: 2861798]

12. Abikoff H, Hechtman L, Klein RG, Gallagher R, Fleiss K, Etcovitch J, Cousins L, Greenfield B, Martin D, Pollack S. Social functioning in children with ADHD treated with long-term methylphenidate and multimodal psychosocial treatment. J Am Acad Child Adolesc Psychiatry. 2004; 43:820–829. [PubMed: 15213583]

13. Newcorn JH, Kratochvil CJ, Allen AJ, Casat CD, Ruff DD, Moore RJ, Michelson D. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry. 2008; 165:721–730. [PubMed: 18281409]

14. Rapoport JL, Buchsbaum MS, Weingartner H, Zahn TP, Ludlow C, Mikkelsen EJ. Dextroamphetamine - Its Cognitive and Behavioral-Effects in Normal and Hyperactive Boys and Normal Men. Archives of General Psychiatry. 1980; 37:933–943. [PubMed: 7406657]

15. Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, Gabrieli JDE. Selective effects of methylphenidate in attention deficit hyperactivity disorder: A functional magnetic resonance study. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95:14494–14499. [PubMed: 9826728]

16. Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW. Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. J Neurosci. 2000; 20:RC65. [PubMed: 10704519]

17. Mehta, MA.; Sahakian, BJ.; Robbins, TW. Comparative psycholpharmacology of methylphenidate and related drugs in human volunteers, patients with ADHD, and experimental animals. In: Solanto, MV.; Arnsten, AFT.; Castellanos, FX., editors. Stimulant Drugs and ADHD: Basic and Clinical Neuroscience. Oxford University Press; New York: 2001. p. 303-331.

18. Rapoport JL, Inoff-Germain G. Responses to methylphenidate in Attention-Deficit/Hyperactivity Disorder and normal children: update 2002. J Atten Disord. 2002; 6:S57–S60. [PubMed: 12685519]

19. Swanson, J.; Volkow, N. Pharmacokinetic and Pharmacodynamic Properties of Methylphenidate in Humans. Oxford University Press; New York, New York: 2001.

20. Kuczenski R, Segal DS. Exposure of adolescent rats to oral methylphenidate: preferential effects on extracellular norepinephrine and absence of sensitization and cross-sensitization to methamphetamine. J Neurosci. 2002; 22:7264–7271. [PubMed: 12177221]

21. Berridge CW, Devilbiss DM, Andrzejewski ME, Arnsten AFT, Kelley AE, Schmeichel B, Hamilton C, Spencer RC. Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. Biol Psychiatry. 2006; 60:1111–1120. [PubMed: 16806100]

22. Zdrale, A.; Meier, TB.; Berridge, CW.; Populin, LC. Effect of methylphenidate on monkey prefrontal cortex-mediated behavior. 2008.

23. Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. Behavioural Brain Research. 1998; 94:127–152. [PubMed: 9708845]

24. Barkley RA, Biederman J. Toward a broader definition of the age-of-onset criterion for attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 1997; 36:1204–1210. [PubMed: 9291721]

25. Arnsten AF. Stimulants: Therapeutic actions in ADHD. Neuropsychopharmacology. 2006; 31:2376–2383. [PubMed: 16855530]

26. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. Nature Reviews Neuroscience. 2002; 3:617–628.

27. Kieling C, Goncalves RR, Tannock R, Castellanos FX. Neurobiology of attention deficit hyperactivity disorder. Child Adolesc Psychiatr Clin N Am. 2008; 17:285–307. viii. [PubMed: 18295147]

28. Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport JL. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A. 2007; 104:19649–19654. [PubMed: 18024590]

29. Bush G, Valera EM, Seidman LJ. Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. Biol Psychiatry. 2005; 57:1273–1284. [PubMed: 15949999]

30. Setlik J, Bond GR, Ho M. Adolescent Prescription ADHD Medication Abuse Is Rising Along With Prescriptions for These Medications. Pediatrics. 2009

31. McCabe SE, Knight JR, Teter CJ, Wechsler H. Non-medical use of prescription stimulants among US college students: prevalence and correlates from a national survey. Addiction. 2005; 100:96–106. [PubMed: 15598197]

32. Maher B. Poll results: look who's doping. Nature. 2008; 452:674–675. [PubMed: 18401370]

33. Kuczenski R, Segal DS. Regional norepinephrine response to amphetamine using dialysis: comparison with caudate dopamine. Synapse. 1992; 11:164–169. [PubMed: 1626314]

34. Kuczenski R, Segal DS, Cho AK, Melega W. Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral responses to the stereoisomers of amphetamine and methamphetamine. J Neurosci. 1995; 15:1308–1317. [PubMed: 7869099]

35. Kuczenski, R.; Segal, DS. Neurochemistry of amphetamine. In: Cho, AK.; Segal, DS., editors. Amphetamine and its analogues: psychopharmacology, toxicology and abuse. Academic Press; San Diego: 1994. p. 81-113.

36. Florin SM, Kuczenski R, Segal DS. Regional extracellular norepinephrine responses to amphetamine and cocaine and effects of clonidine pretreatment. Brain Res. 1994; 654:53–62. [PubMed: 7982098]

37. Kuczenski R, Segal DS. Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. J Neurochem. 1997; 68:2032–2037. [PubMed: 9109529]

38. Kuczenski R, Segal DS. Locomotor effects of acute and repeated threshold doses of amphetamine and methylphenidate: relative roles of dopamine and norepinephrine. J Pharmacol Exp Ther. 2001; 296:876–883. [PubMed: 11181919]

39. Drouin C, Page M, Waterhouse B. Methylphenidate enhances noradrenergic transmission and suppresses mid- and long-latency sensory responses in the primary somatosensory cortex of awake rats. J Neurophysiol. 2006; 96:622–632. [PubMed: 16687613]

40. Carboni E, Tanda GL, Frau R, Di CG. Blockade of the noradrenaline carrier increases extracellular dopamine concentrations in the prefrontal cortex: evidence that dopamine is taken up in vivo by noradrenergic terminals. J Neurochem. 1990; 55:1067–1070. [PubMed: 2117046]

41. Sesack SR, Hawrylak VA, Matus C, Guido MA, Levey AI. Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex exhibit sparse immunoreactivity for the dopamine transporter. J Neurosci. 1998; 18:2697–2708. [PubMed: 9502827]

42. Dalley JW, Cardinal RN, Robbins TW. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neurosci Biobehav Rev. 2004; 28:771–784. [PubMed: 15555683]

43. Pratt WE, Mizumori SJ. Neurons in rat medial prefrontal cortex show anticipatory rate changes to predictable differential rewards in a spatial memory task. Behav Brain Res. 2001; 123:165–183. [PubMed: 11399329]

44. Johnson A, van der Meer MA, Redish AD. Integrating hippocampus and striatum in decision-making. Curr Opin Neurobiol. 2007; 17:692–697. [PubMed: 18313289]

45. Voorn P, Vanderschuren LJ, Groenewegen HJ, Robbins TW, Pennartz CM. Putting a spin on the dorsal-ventral divide of the striatum. Trends Neurosci. 2004; 27:468–474. [PubMed: 15271494]

46. Gabbott PL, Warner TA, Jays PR, Salway P, Busby SJ. Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. J Comp Neurol. 2005; 492:145–177. [PubMed: 16196030]

47. Volkow ND, Wang GJ, Fowler JS, Logan J, Franceschi D, Maynard L, Ding YS, Gatley SJ, Gifford A, Zhu W, Swanson JM. Relationship between blockade of dopamine transporters by oral methylphenidate and the increases in extracellular dopamine: therapeutic implications. Synapse. 2002; 43:181–187. [PubMed: 11793423]

48. Kelly PH, Seviour PW, Iversen SD. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res. 1975; 94:507–522. [PubMed: 1171714]

49. Carr GD, White NM. Anatomical disassociation of amphetamine's rewarding and aversive effects: an intracranial microinjection study. Psychopharmacology (Berl). 1986; 89:340–346. [PubMed: 3088661]

50. Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. Psychol Rev. 1987; 94:469–492. [PubMed: 3317472]

51. Kelley AE, Gauthier AM, Lang CG. Amphetamine microinjections into distinct striatal subregions cause dissociable effects on motor and ingestive behavior. Behav Brain Res. 1989; 35:27–39. [PubMed: 2803542]

52. Berridge CW. Neural substrates of psychostimulant-induced arousal. Neuropsychopharmacology. 2006; 31:2332–2340. [PubMed: 16855535]

53. Berridge CW. Noradrenergic modulation of arousal. Brain Res Rev. 2008; 58:1–17. [PubMed: 18199483]

54. Biederman J. Pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD) decreases the risk for substance abuse: findings from a longitudinal follow-up of youths with and without ADHD. J Clin Psychiatry. 2003; 64(Suppl 11):3–8. [PubMed: 14529323]

55. Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/ hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics. 2003; 111:179–185. [PubMed: 12509574]

56. Berridge CW, Waterhouse BD. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Brain Res Rev. 2003; 42:33–84. [PubMed: 12668290]

57. Clayton EC, Rajkowski J, Cohen JD, ston-Jones G. Phasic activation of monkey locus ceruleus neurons by simple decisions in a forced-choice task. J Neurosci. 2004; 24:9914–9920. [PubMed: 15525776]

58. Arnsten AFT, Li BM. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol Psychiatry. 2005; 57:1377–1384. [PubMed: 15950011]

59. Berridge, CW. The Locus Coeruleus-Noradrenergic System and Stress: Implications for Post-Traumatic Stress Disorder (PTSD). In: Shiromani, PJ.; Keane, TM.; Ledoux, JE., editors. Posttraumatic Stress Disorder: Basic Science and Clinical Practice. Humana/Springer; New York, NY: 2008.

60. Devilbiss DM, Waterhouse BD. Phasic and Tonic Patterns of Locus Coeruleus Output Differentially Modulate Sensory Network Function in the Awake Rat. PLoS One. 2010

61. Hurley LM, Devilbiss DM, Waterhouse BD. A matter of focus: monoaminergic modulation of stimulus coding in mammalian sensory networks. Curr Opin Neurobiol. 2004; 14:488–495. [PubMed: 15321070]

62. Pitts DK, Marwah J. Electrophysiological actions of cocaine on noradrenergic neurons in rat locus ceruleus. J Pharmacol Exp Ther. 1987; 240:345–351. [PubMed: 3806395]

63. Curtis AL, Conti E, Valentino RJ. Cocaine effects on brain noradrenergic neurons of anesthetized and unanesthetized rats. Neuropharmacology. 1993; 32:419–428. [PubMed: 8321424]

64. Devilbiss DM, Berridge CW. Low-dose methylphenidate actions on tonic and phasic locus coeruleus discharge. J Pharmacol Exp Ther. 2006; 319:1327–1335. [PubMed: 16980569]

65. Agnati LF, Guidolin D, Guescini M, Genedani S, Fuxe K. Understanding wiring and volume transmission. Brain Res Rev. 2010; 64:137–159. [PubMed: 20347870]

66. Devilbiss, DM.; Waterhouse, BD. Effects of tonic versus phasic activation of the locus coeruleus on thalamic and cortical neuronal responsiveness to afferent pathway stimulation. Society for Neuroscience; Washington, DC: 2002.

67. Devilbiss DM, Waterhouse BD. The effects of tonic locus ceruleus output on sensory-evoked responses of ventral posterior medial thalamic and barrel field cortical neurons in the awake rat. J Neurosci. 2004; 24:10773–10785. [PubMed: 15574728]

68. Miner LH, Schroeter S, Blakely RD, Sesack SR. Ultrastructural localization of the norepinephrine transporter in superficial and deep layers of the rat prelimbic prefrontal cortex and its spatial relationship to probable dopamine terminals. J Comp Neurol. 2003; 466:478–494. [PubMed: 14566944]

69. Eckhoff P, Wong-Lin KF, Holmes P. Optimality and robustness of a biophysical decision-making model under norepinephrine modulation. J Neurosci. 2009; 29:4301–4311. [PubMed: 19339624]

70. Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci. 2005; 28:403–450. [PubMed: 16022602]

71. Bouret S, Sara SJ. Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci. 2005; 28:574–582. [PubMed: 16165227]

72. Clark L, Blackwell AD, Aron AR, Turner DC, Dowson J, Robbins TW, Sahakian BJ. Association between response inhibition and working memory in adult ADHD: a link to right frontal cortex pathology? Biol Psychiatry. 2007; 61:1395–1401. [PubMed: 17046725]

73. Lundqvist, T. Imaging Cognitive Deficits in Drug Abuse. Vol. 3. Springer-Verlag; Berlin: 2009.

74. Green WH. Nonstimulant drugs in the treatment of attention-deficit hyperactivity disorder. Child and Adolescent Psychiatric Clinics of North America. 1992; 1:449–465.

75. Baldessarini, RJ. Chemotherapy in Psychiatry. Harvard University Press; Cambridge, MA: 1985. Antidepressant Agents; p. 130-234.

76. Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. Life Sci. 1993; 52:1023–1029. [PubMed: 8445992]

77. Biederman J, Baldessarini RJ, Wright V, Knee D, Harmatz JS. A double-blind placebo controlled study of desipramine in the treatment of ADD: I. Efficacy. J Am Acad Child Adolesc Psychiatry. 1989; 28:777–784. [PubMed: 2676967]

78. Gastfriend DR, Biederman J, Jellinek MS. Desipramine in the treatment of attention deficit disorder in adolescents. Psychopharmacol Bull. 1985; 21:144–145. [PubMed: 3983334]

79. Rapoport JL, Zametkin A, Donnelly M, Ismond D. New drug trials in attention deficit disorder. Psychopharmacol Bull. 1985; 21:232–236. [PubMed: 3923528]

80. Spencer T, Biederman J, Kerman K, Steingard R, Wilens T. Desipramine treatment of children with attention-deficit hyperactivity disorder and tic disorder or Tourette's syndrome. J Am Acad Child Adolesc Psychiatry. 1993; 32:354–360. [PubMed: 8444765]

81. Prince JB, Wilens TE, Biederman J, Spencer TJ, Millstein R, Polisner DA, Bostic JQ. A controlled study of nortriptyline in children and adolescents with attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol. 2000; 10:193–204. [PubMed: 11052409]

82. Wong DT, Threlkeld PG, Best KL, Bymaster FP. A new inhibitor of norepinephrine uptake devoid of affinity for receptors in rat brain. J Pharmacol Exp Ther. 1982; 222:61–65. [PubMed: 6123593]

83. Gastfriend DR, Biederman J, Jellinek MS. Desipramine in the treatment of adolescents with attention deficit disorder. Am J Psychiatry. 1984; 141:906–908. [PubMed: 6375400]

84. Spencer T, Biederman J, Wilens T, Prince J, Hatch M, Jones J, Harding M, Faraone SV, Seidman L. Effectiveness and tolerability of tomoxetine in adults with attention deficit hyperactivity disorder. Am J Psychiatry. 1998; 155:693–695. [PubMed: 9585725]

85. Michelson D, Adler L, Spencer T, Reimherr FW, West SA, Allen AJ, Kelsey D, Wernicke J, Dietrich A, Milton D. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biol Psychiatry. 2003; 53:112–120. [PubMed: 12547466]

86. Zerbe RL, Rowe H, Enas GG, Wong D, Farid N, Lemberger L. Clinical pharmacology of tomoxetine, a potential antidepressant. J Pharmacol Exp Ther. 1985; 232:139–143. [PubMed: 3965689]

87. Chamberlain SR, Del CN, Dowson J, Muller U, Clark L, Robbins TW, Sahakian BJ. Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. Biol Psychiatry. 2007; 62:977–984. [PubMed: 17644072]

88. Seu E, Lang A, Rivera RJ, Jentsch JD. Inhibition of the norepinephrine transporter improves behavioral flexibility in rats and monkeys. Psychopharmacology (Berl). 2009; 202:505–519. [PubMed: 18604598]

89. Bymaster FP, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH, Morin SM, Gehlert DR, Perry KW. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: A potential mechanism for efficacy in Attention Deficit/Hyperactivity Disorder. Neuropsychopharmacology. 2002; 27:699–711. [PubMed: 12431845]

90. Horn AS. Structure-activity relations for the inhibition of catecholamine uptake into synaptosomes from noradrenaline and dopaminergic neurones in rat brain homogenates. Br J Pharmacol. 1973; 47:332–338. [PubMed: 4722047]

91. Raiteri M, del CR, Bertollini A, Levi G. Effect of sympathomimetic amines on the synaptosomal transport of noradrenaline, dopamine and 5-hydroxytryptamine. Eur J Pharmacol. 1977; 41:133–143. [PubMed: 832672]

92. Arnsten AF. Stress impairs prefrontal cortical function in rats and monkeys: role of dopamine D1 and norepinephrine alpha-1 receptor mechanisms. Prog Brain Res. 2000; 126:183–192. [PubMed: 11105647]

93. MacDonald E, Kobilka BK, Scheinin M. Gene targeting--homing in on alpha 2-adrenoceptor-subtype function. Trends Pharmacol Sci. 1997; 18:211–219. [PubMed: 9227000]

94. Hunt RD, Minderaa RB, Cohen DJ. Clonidine benefits children with attention deficit disorder and hyperactivity: report of a double-blind placebo-crossover therapeutic trial. J Am Acad Child Psychiatry. 1985; 24:617–629. [PubMed: 3900182]

95. Hunt RD, Arnsten AFT, Asbell MD. An open trial of guanfacine in the treatment of attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 1995; 34:50–54. [PubMed: 7860456]

96. Scahill L, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, Arnsten AFT, Cohen DJ, Leckman JF. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. Am J Psychiatry. 2001; 158:1067–1074. [PubMed: 11431228]

97. Biederman J, Melmed RD, Patel A, McBurnett K, Konow J, Lyne A, Scherer N. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics. 2008; 121:e73–e84. [PubMed: 18166547]

98. Jakala P, Riekkinen M, Sirvio J, Koivisto E, Kejonen K, Vanhanen M, Riekkinen P Jr. Guanfacine, but not clonidine, improves planning and working memory performance in humans. Neuropsychopharmacology. 1999; 20:460–470. [PubMed: 10192826]

99. Franowicz JS, Arnsten AF. The alpha-2a noradrenergic agonist, guanfacine, improves delayed response performance in young adult rhesus monkeys. Psychopharmacology (Berl). 1998; 136:8–14. [PubMed: 9537677]

100. Mao ZM, Arnsten AFT, Li BM. Local infusion of an alpha-1 adrenergic agonist into the prefrontal cortex impairs spatial working memory performance in monkeys. Biol Psychiatry. 1999; 46:1259–1265. [PubMed: 10560031]

101. Steere JC, Arnsten AF. The alpha-2A noradrenergic receptor agonist guanfacine improves visual object discrimination reversal performance in aged rhesus monkeys. Behav Neurosci. 1997; 111:883–891. [PubMed: 9383511]

102. Avery RA, Franowicz JS, Studholme C, van Dyck CH, Arnsten AF. The alpha-2A-adrenoceptor agonist, guanfacine, increases regional cerebral blood flow in dorsolateral prefrontal cortex of monkeys performing a spatial working memory task. Neuropsychopharmacology. 2000; 23:240–249. [PubMed: 10942848]

103. Berridge CW, Arnsten AFT, Foote SL. Noradrenergic modulation of cognitive function: clinical implications of anatomical, electrophysiological and behavioural studies in animal models [editorial]. Psychol Med. 1993; 23:557–564. [PubMed: 8234565]

104. Wang M, Ramos BP, Paspalas CD, Shu Y, Simen A, Duque A, Vijayraghavan S, Brennan A, Dudley A, Nou E, Mazer JA, McCormick DA, Arnsten AF. Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. Cell. 2007; 129:397–410. [PubMed: 17448997]

105. Shenker A. The mechanism of action of drugs used to treat attention-deficit hyperactivity disorder: focus on catecholamine receptor pharmacology. Adv Pediatr. 1992; 39:337–382. [PubMed: 1359740]

106. Wender PH, Wood DR, Reimherr FW, Ward M. An open trial of pargyline in the treatment of attention deficit disorder, residual type. Psychiatry Res. 1983; 9:329–336. [PubMed: 6359210]

107. Zametkin AJ, Rapoport JL. Neurobiology of attention deficit disorder with hyperactivity: where have we come in 50 years? J Am Acad Child Adolesc Psychiatry. 1987; 26:676–686. [PubMed: 2889717]

108. Mefford IN, Potter WZ. A neuroanatomical and biochemical basis for attention deficit disorder with hyperactivity in children: a defect in tonic adrenaline mediated inhibition of locus coeruleus stimulation. Med Hypotheses. 1989; 29:33–42. [PubMed: 2546021]

109. Yang CR, Seamans JK, Gorelova N. Developing a neuronal model for the pathophysiology of schizophrenia based on the nature of electrophysiological actions of dopamine in the prefrontal cortex. Neuropsychopharmacology. 1999; 21:161–194. [PubMed: 10432466]

110. Lewis, DA. The catecholamine innervation of primate cerebral cortex. In: Solanto, MV.; Arnsten, AFT.; Castellanos, FX., editors. Stimulant Drugs and ADHD: Basic and Clinical Neuroscience. Oxford University Press; New York: 2001. p. 77-103.

111. Paspalas CD, Goldman-Rakic PS. Microdomains for dopamine volume neurotransmission in primate prefrontal cortex. J Neurosci. 2004; 24:5292–5300. [PubMed: 15190100]

112. Van Tol HH, Bunzow JR, Guan HC, Sunahara RK, Seeman P, Niznik HB, Civelli O. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. Nature. 1991; 350:610–614. [PubMed: 1840645]

113. Arnsten AF. Catecholamine and second messenger influences on prefrontal cortical networks of "representational knowledge": a rational bridge between genetics and the symptoms of mental illness. Cereb Cortex. 2007; 17(Suppl 1):i6–15. [PubMed: 17434919]

114. Postle BR. Working memory as an emergent property of the mind and brain. Neuroscience. 2006; 139:23–38. [PubMed: 16324795]

115. Arnsten AFT, Steere JC, Hunt RD. The contribution of alpha 2-noradrenergic mechanisms of prefrontal cortical cognitive function. Potential significance for attention- deficit hyperactivity disorder. Arch Gen Psychiatry. 1996; 53:448–455. [PubMed: 8624188]

116. Birnbaum S, Gobeske KT, Auerbach J, Taylor JR, Arnsten AF. A role for norepinephrine in stress-induced cognitive deficits: alpha-1- adrenoceptor mediation in the prefrontal cortex. Biol Psychiatry. 1999; 46:1266–1274. [PubMed: 10560032]

117. Birnbaum SG, Yuan PX, Wang M, Vijayraghavan S, Bloom AK, Davis DJ, Gobeske KT, Sweatt JD, Manji HK, Arnsten AF. Protein kinase C overactivity impairs prefrontal cortical regulation of working memory. Science. 2004; 306:882–884. [PubMed: 15514161]

118. Ramos BP, Colgan L, Nou E, Ovadia S, Wilson SR, Arnsten AF. The beta-1 adrenergic antagonist, betaxolol, improves working memory performance in rats and monkeys. Biol Psychiatry. 2005; 58:894–900. [PubMed: 16043136]

119. Ramos BP, Colgan LA, Nou E, Arnsten AF. Beta2 adrenergic agonist, clenbuterol, enhances working memory performance in aging animals. Neurobiol Aging. 2008; 29:1060–1069. [PubMed: 17363115]

120. Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci. 2007; 10:376–384. [PubMed: 17277774]

121. Fuster JM, Alexander GE. Neuron activity related to short-term memory. Science. 1971; 173:652–654. [PubMed: 4998337]

122. Funahashi S, Bruce CJ, Goldman-Rakic PS. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J Neurophysiol. 1989; 61:331–349. [PubMed: 2918358]

123. Smiley JF, Williams SM, Szigeti K, Goldman-Rakic PS. Light and electron microscopic characterization of dopamine-immunoreactive axons in human cerebral cortex. J Comp Neurol. 1992; 321:325–335. [PubMed: 1506472]

124. Lapiz MD, Morilak DA. Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. Neuroscience. 2006; 137:1039–1049. [PubMed: 16298081]

125. Winsberg BG, Camp-Bruno JA, Vink J, Timmer CJ, Sverd J. Mianserin pharmacokinetics and behavior in hyperkinetic children. J Clin Psychopharmacol. 1987; 7:143–147. [PubMed: 3597800]

126. Bobb AJ, Addington AM, Sidransky E, Gornick MC, Lerch JP, Greenstein DK, Clasen LS, Sharp WS, Inoff-Germain G, Wavrant-De VF, rcos-Burgos M, Straub RE, Hardy JA, Castellanos FX, Rapoport JL. Support for association between ADHD and two candidate genes: NET1 and DRD1. Am J Med Genet B Neuropsychiatr Genet. 2005; 134B:67–72. [PubMed: 15717291]

127. Daly G, Hawi Z, Fitzgerald M, Gill M. Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. Mol Psychiatry. 1999; 4:192–196. [PubMed: 10208453]

128. Roman T, Schmitz M, Polanczyk GV, Eizirik M, Rohde LA, Hutz MH. Further evidence for the association between attention-deficit/hyperactivity disorder and the dopamine-beta-hydroxylase gene. Am J Med Genet. 2002; 114:154–158. [PubMed: 11857576]

129. Bellgrove MA, Hawi Z, Gill M, Robertson IH. The cognitive genetics of attention deficit hyperactivity disorder (ADHD) sustained attention as a candidate phenotype. Cortex. 2006; 42:838–845. [PubMed: 17131588]

130. Kieling C, Genro JP, Hutz MH, Rohde LA. The −1021 C/T DBH polymorphism is associated with neuropsychological performance among children and adolescents with ADHD. Am J Med Genet B Neuropsychiatr Genet. 2008; 147B:485–490. [PubMed: 18081028]

131. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. Hum Genet. 2009; 126:51–90. [PubMed: 19506906]

132. Mill J, Caspi A, Williams BS, Craig I, Taylor A, Polo-Tomas M, Berridge CW, Poulton R, Moffitt TE. Prediction of heterogeneity in intelligence and adult prognosis by genetic polymorphisms in the dopamine system among children with attention-deficit/hyperactivity disorder: evidence from 2 birth cohorts. Arch Gen Psychiatry. 2006; 63:462–469. [PubMed: 16585476]
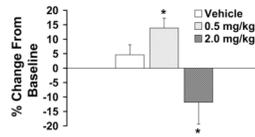
Figure 1.
Low-dose psychostimulants elicit an inverted-U shaped dose-dependent modulation of PFC-dependent behavior. Shown are the effects of varying doses of intraperitoneally administered methylphenidate on performance in a delayed-response task of spatial working memory. Methylphenidate improves performance in this task at doses that produce similar and clinically-relevant plasma concentrations (0.5 mg/kg; orally; 21). At higher doses, performance is impaired, resulting in an inverted-U shaped dose response curve. In this task, animals were rewarded (chocolate chip) for entering the arm of a t-maze not entered on the previous trial. Between trials animals were held in a start box for a delay (range = 10–120 secs) titrated so that baseline accuracy is 70–80%. Baseline performance was defined as the average performance from the two days immediately preceding drug testing. A similar facilitation of performance in this task was observed with oral administration of a cognition-enhancing dose of methylphenidate that produced plasma concentrations comparable to those seen with intraperitoneal administration of 0.5 mg/kg methylphenidate (2.0 mg/kg; 21). Data are mean performance (± SEM) across the 10 trials, expressed as percent correct. $^{*}P < 0.01$ relative to baseline performance. Modified from (6,21).
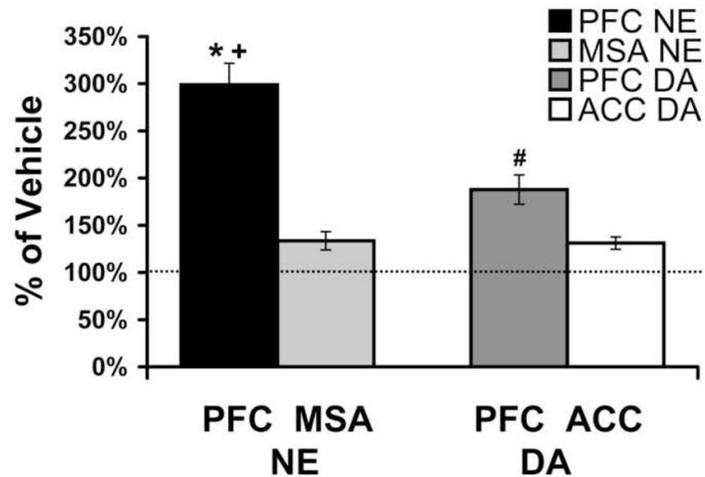
Figure 2.
Cognition-enhancing doses of methylphenidate increase extracellular NE and DA preferentially within the PFC. Shown are the effects of a cognition-enhancing dose of MPH that produces clinically-relevant peak plasma concentrations (0.5 mg/kg, intraperitoneally) on extracellular levels of NE and DA in the PFC, NE in the medial septal area (MSA), and DA in the nucleus accumbens core (ACC). Data are an average of two 15-minute samples colleted 15–45 minutes following drug treatment and are expressed as percent of vehicle-treatment. At this dose, MPH produced only a modest (~30%) increase in NE and DA levels outside the PFC. In contrast, within the PFC, this dose of MPH produced a substantially larger increase in NE and DA levels. Moreover, the increase in PFC NE levels (~200%) was significantly larger than that seen for PFC DA (~85%). A similar pattern of effects was observed with oral administration of a cognition-enhancing dose (2.0 mg/kg) of methylphenidate that produced plasma concentrations comparable to those seen with intraperitoneal administration of 0.5 mg/kg methylphenidate. [*]$P < 0.001$ relative to MSA NE; [+]$P < 0.001$ relative to PFC DA, [#]$P < 0.05$ relative to ACC DA. Modified from (21).
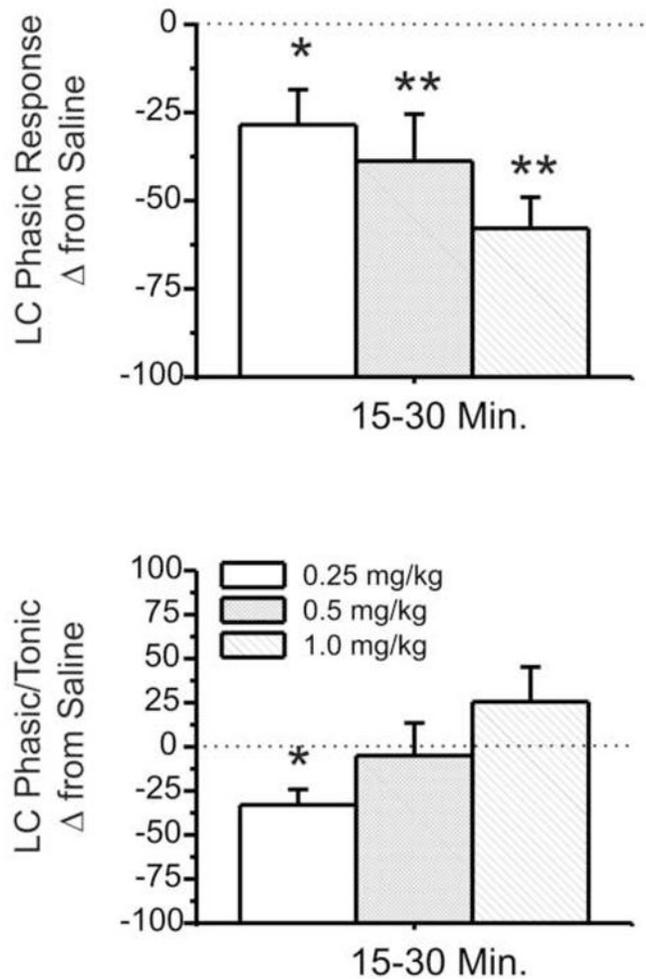
Figure 3.
Cognition-enhancing doses of methylphenidate exert a modest influence on tonic and phasic LC discharge. Shown are the effects of varying doses of methylphenidate (intraperitoneally) on the magnitude of LC phasic discharge in the halothane-anesthetized rat (see 64). Doses examined included the cognition-enhancing dose of 0.5 mg/kg. Evoked discharge was elicited by brief electrical stimulation of the foot. For all treatments, data were normalized by calculating the percent change from pre-drug conditions and then expressed as a change from vehicle (saline). **Panel A** depicts the effects of low-dose methylphenidate on the magnitude of phasic LC discharge, expressed as a change from saline treatment, for a 15-minute epoch that began 15-minutes following drug treatment (n=60 stimulus presentations). Methylphenidate produced a dose-dependent decrease in phasic discharge that was relatively mild at the 0.5 mg/kg dose. **Panel B** depicts the effects of methylphenidate on the signal-to-noise ratio of phasic responses (relative to tonic discharge). Because methylphenidate-induced suppression of phasic discharge was associated with a similar magnitude suppression of tonic discharge, methylphenidate had minimal effects on the signal-to-noise ratio for phasic discharge, particularly at the 0.5 mg/kg dose. Similar effects were observed with oral methylphenidate administration (see 64). $^{*}P < 0.05$, $^{**}P < 0.01$ relative to saline-controls. Modified from (64).
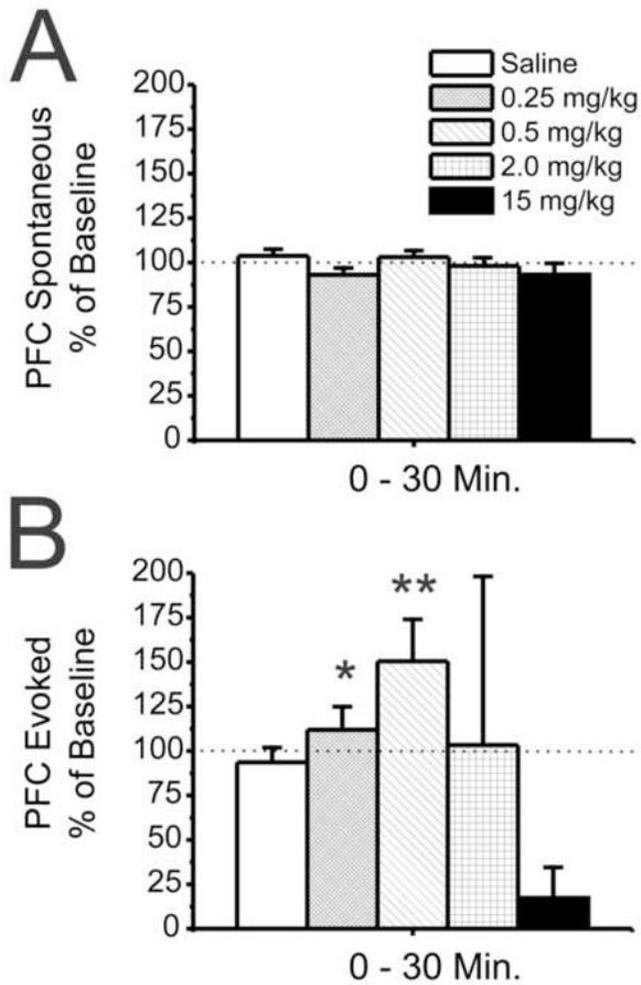
Figure 4.
Cognition-enhancing doses of methylphenidate preferentially increase the responsiveness of PFC neurons. Shown are the effects of varying doses of methylphenidate on spontaneous discharge and excitatory evoked-responses (elicited by brief electrical stimulation of the hippocampus) of PFC neurons in the awake-freely moving rat. Doses examined included the cognition-enhancing dose of 0.5 mg/kg (see 6). All data are expressed as the percent change from pre-drug conditions. **Panel A**: Spontaneous discharge of PFC neurons was minimally affected by low doses of methylphenidate. **Panel B**: Hippocampal stimulus-evoked excitatory discharge in PFC neurons exhibited a dose-dependent inverted-U facilitation/ suppression. The maximal facilitation of PFC responses to hippocampal input was observed following the 0.5 mg/kg dose. A behaviorally-activating, dose of MPH (15.0 mg/kg) resulted in a suppression of stimulus-evoked activity well below baseline levels. $^{*}P <$ 0.05, $^{**}P < 0.01$ relative to baseline. Modified from (6).