THE ANATOMICAL RECORD 294:1698–1712 (2011)

Experimental Strategies for Investigating Psychostimulant Drug Actions and Prefrontal Cortical Function in ADHD and Related Attention Disorders

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ABSTRACT

Amphetamine-like psychostimulant drugs have been used for decades to treat a variety of clinical conditions. Methylphenidate (MPH)—Ritalin^{R}, a compound that blocks reuptake of synaptically released norepinephrine (NE) and dopamine (DA) in the brain, has been used for more than 30 years in low dose, long-term regimens to treat attention deficit-hyperactive disorder (ADHD) in juveniles, adolescents, and adults. Now, these agents are also becoming increasingly popular among healthy individuals from all walks of life (e.g., military, students) and age groups (teenagers thru senior citizens) to promote wakefulness and improve attention. Although there is agreement regarding the primary biochemical action of MPH, the physiological basis for its efficacy in normal individuals and ADHD patients is lacking. Study of the behavioral and physiological actions of clinically and behaviorally relevant doses of MPH in normal animals provides an opportunity to explore the role of catecholamine transmitters in prefrontal cortical function and attentional processes as they relate to normal operation of brain circuits and ADHD pathology. The goal of ongoing studies has been to: (1) assess the effects of low dose MPH on rodent performance in a well characterized sensory-guided sustained attention task, (2) examine the effects of the same low-dose chronic MPH administration on task-related discharge of prefrontal cortical (PFC) neurons, and (3) investigate the effects of NE and DA on membrane response properties and synaptic transmission in identified subsets of PFC neurons. Combinations of these approaches can be used in adolescent, adult, and aged animals to identify the parameters of cell and neural circuit function that are regulated by MPH and to establish an overarching explanation of how MPH impacts PFC operations from cellular through behavioral functional domains. Anat Rec, 294:1698–1712, 2011. © 2011 Wiley-Liss, Inc.

Grant sponsors: NIDA, NIMH, National Science Foundation, Drexel Translational Foundation Grant (PA Tobacco Formula Funds), Drexel Human Cognition Enhancement Program, Wisconsin Institutes of Discovery, University of Wisconsin Graduate School; Grant numbers: DA0917960, DA000389, MH14602, MH081843, MH084474, NSF 0918555.

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Received 17 June 2010; Accepted 14 February 2011

DOI 10.1002/ar.21403

Published online 8 September 2011 in Wiley Online Library (wileyonlinelibrary.com).

Key words: methylphenidate; psychostimulant; behavioral pharmacology; catecholamines; dopamine; norepinephrine; attention deficit hyperactivity disorder

Amphetamine-like psychostimulant drugs have been used for decades to treat a variety of clinical conditions. For example, methylphenidate (MPH)—Ritalin^{R}, a compound that blocks reuptake of synaptically released norepinephrine (NE) and dopamine (DA) in the brain, has been used for more than 70 years in low dose, long-term regimens to treat attention deficit hyperactivity disorder (ADHD) in juveniles, adolescents, and adults. These agents are also becoming increasingly popular among healthy individuals from all walks of life (e.g., military, students) and age groups (teenagers through senior citizens) to promote wakefulness and generally enhance cognitive function (Repantis et al., 2010). Although there is general agreement regarding the primary pharmacological action of MPH, the physiological bases for its efficacy in normal individuals and ADHD patients are unclear. Recent studies have employed combinations of behavioral, electrophysiological, and neurochemical assays to study the actions of clinically relevant doses of MPH in normal animals and ADHD models. This work, which is reviewed here, begins to provide insights regarding the role of catecholamine transmitters in prefrontal cortical function and attentional processes as they relate to dynamic operation of brain circuits under normal and abnormal (e.g., ADHD) conditions.

AMPHETAMINE-LIKE STIMULANTS AND METHYLPHENIDATE

Pharmacology of Amphetamine-Like Psychostimulants

Surprisingly, little is known about the neural actions responsible for the cognition-enhancing/therapeutic actions of amphetamine-like psychostimulants, in general, and MPH, in particular. Although it is clear that amphetamine-like stimulants release or block reuptake of catecholamine transmitters and thus elevate extracellular NE and DA in brain tissue, the impact of elevated levels of these catecholamines on neuronal function and signal transmission in the brain can only be inferred from what is still an incomplete understanding of the physiology of these important transmitter systems. Furthermore, despite substantial evidence of both quantitative and qualitative differences in drug action with dosage (Kuczenski and Segal, 2001), nearly all our understanding of the neurobiology of psychostimulants derives from studies of abuse or addiction, where only high doses—much higher than those used clinically—are employed. Because of the established roles of NE and DA systems in cognition, attention, and sensory signal processing and because of the prominent innervation of prefrontal cortex (PFC) networks by NE and DA systems, the major focus of recent investigations has been on low-dose drug actions and behaviors that engage this brain region.

Behavioral Actions of Amphetamine-Like Stimulants

Amphetamine-like stimulants elicit a variety of dose-dependent behavioral effects. At lower doses, increased arousal and enhanced focused attention predominate. At high doses, a variety of effects emerges, including euphoria, locomotor activation, and at the highest doses, intense motor stereotypies and/or psychoses (Randrup and Munkvad, 1966; Segal, 1975; Haber et al., 1981; Rebec and Bashore, 1984). It is important to note that the ability of low-dose stimulants to increase sustained attention, improve response inhibition and decrease locomotor activity is not unique to patients with ADHD. All of these actions are observed in non-ADHD humans and normal animals (Rapoport et al., 1980; Vaidya et al., 1998; Mehta, 2001; Kuczenski and Segal, 2002). In addition, the effects of low-dose MPH on PFC neuronal activity (assessed by functional MRI) in a go/no-go task are similar in ADHD patients and normal control subjects (Vaidya et al., 1998). Thus, the therapeutic actions of stimulants used to treat ADHD are neither unique to ADHD patients nor dependent on pathology within catecholaminergic systems in ADHD. Similar evidence exists to validate investigations of MPH actions in normal, experimental animals.

Early observations that amphetamine increases DA and NE neurotransmission stimulated intense inquiry into the roles of these neurotransmitters in the behavioral actions of these drugs (see Moore, 1978). Using selective NE and DA receptor agonists and antagonists, it was demonstrated that DA is critically involved in the reinforcing (Wise, 1987; Koob and Bloom, 1988), locomotor-enhancing (Randrup and Munkvad, 1966), and stereotypy-inducing (Kelly et al., 1975) effects of amphetamine. The degree to which NE participates in the behavioral effects of moderate stimulant doses remains in question; however, evidence now suggests a prominent role for NE in the arousal-, reinforcing-, locomotor-, and startle-enhancing effects that predominate at lower doses, but not the stereotypy-inducing effects observed at higher doses of these drugs (Creese and Iversen, 1975; Kokkinidis and Anisman, 1978; Ogren et al., 1983; Mavridis et al., 1991; Blanc et al., 1994; Berridge and Morris, 2000; Drouin et al., 2002; Drouin et al., 2006).

Dose-Dependent Effects of Amphetamine-Like Stimulants

It is important to note that the qualitative and quantitative neurochemical/pharmacological actions of amphetamine-like stimulants are influenced strongly by: (1) identity of the drug, (2) dose of drug, and (3) selectivity of drug action. First, different amphetamine derivatives vary in the extent to which they affect different monoamine systems. For example, serotonergic systems are

relatively insensitive to even moderate to high doses (10–30 mg/kg, sc) of MPH (Kuczenski et al., 1995). This stands in contrast to the particularly potent actions of MPH on NE efflux at these and substantially lower doses (Kuczenski, 1994; Kuczenski et al., 1995). This difference suggests that the therapeutic action of MPH in the treatment of ADHD and in off-label applications most likely does not involve alterations in extracellular levels of serotonin. Second, there is a variety of dose-dependent effects of these drugs. For example, amphetamine both stimulates DA efflux from the axon terminal and inhibits DA reuptake across a wide range of doses (Kuczenski, 1994). In contrast, at lower doses (0.5–2.0 mg/kg, s.c.) amphetamine acts primarily as an inhibitor of NE reuptake (Florin et al., 1994; Kuczenski et al., 1995). Combined, these observations indicate that it is inappropriate to draw conclusions about MPH actions in behavioral tasks and PFC function without careful consideration of dose-response relationships and potentially unique properties of individual amphetamine derivatives.

Amphetamine-Like Stimulants and Treatment of ADHD

ADHD is a childhood cognitive disorder that can extend into adulthood. It is characterized by inattentiveness and/or hyperactivity and impulsiveness. Patients with ADHD are at substantial risk for social, academic, and occupational dysfunction. The central difficulty associated with ADHD appears to be in the volitional control of attention and impulsivity during activities that are monotonous and effortful and/or that lack inherent reward (see review, Solanto, 2001). ADHD patients are also easily distracted by environmental stimuli that would otherwise be ignored. Thus, inappropriate sensory signal processing and attention to task are core deficits in these individuals. Currently, pharmacological treatment with amphetamine-like stimulants is the most effective form of therapy (for review, Greenhill, 2001), with MPH (Ritalin) being the most widely prescribed (70%) agent for the treatment of ADHD (Greenhill, 2001; Swanson, 2001). Therapeutic effects of MPH are observed when plasma levels of ~8–40 ng/mL are achieved, with a maximum efficacy achieved near 10 ng/mL (see review—Swanson, 2001). MPH and related agents ameliorate the core symptoms of inattentiveness, hyperactivity, and impulsivity in 75–95% of ADHD individuals (see review, Solanto, 2001), but are associated with a variety of undesired side effects, including toxicity, growth retardation, and sleep disruption, as well as increased opportunity for illegal distribution for recreational/abuse purposes (see review, Greenhill, 2001). Thus, the development of new pharmacological therapies that do not involve amphetamine-like stimulants is a highly desirable endpoint. Towards this end, it is essential that we understand the neural mechanisms that underlie the therapeutic efficacy of these compounds in the treatment of ADHD.

Relationship Between Experimental and Therapeutic Doses of MPH

The above observations indicate it is inappropriate to postulate neuronal mechanisms of therapeutic action of MPH in ADHD on the basis of observations made with (1) psychostimulants not used in the treatment of ADHD or (2) doses of MPH that exceed the dose range used clinically. Thus, in experimental studies it is important to use doses of MPH that result in clinically relevant plasma concentrations (Wargin et al., 1983; Berridge et al., 2006) and that produce behaviorally relevant actions (Berridge et al., 2006).

CATECHOLAMINES, COGNITION, AND ATTENTION

Behavioral/Cognitive Actions of NE and DA

Both NE and DA are involved in a variety of attention, memory, and behavioral processes via a multiplicity of actions at multiple receptors, and both are thought to figure prominently in the therapeutic actions of amphetamine-like stimulants in ADHD (for review, Solanto, 1998). Numerous studies have focused on these two catecholamine systems but a complete accounting of this literature is beyond the scope of this review. Given that NE and DA systems share a variety of features, and due to space constraints, the following overview focuses on the locus coeruleus (LC)-NE network as a model system followed by a less extensive review of DA systems.

ADHD, MPH, and the LC-NE System

MPH blocks reuptake of both NE and DA. Noradrenergic α_2-agonists, particularly post-synaptic selective agonists, such as guanfacine, as well as selective NE reuptake inhibitors are also effective in the treatment of ADHD (see review Pliszka, 2001). Combined, these observations indicate that one mechanism shared by a variety of pharmacological treatments for ADHD is the enhancement of noradrenergic neurotransmission. In this context, it is significant that the LC is the primary source of NE in the forebrain. LC neurons are extremely sensitive to salient sensory stimuli, and sensory-driven LC activity appears to participate in attention processes (see reviews—Foote et al., 1983; Berridge and Waterhouse, 2003). In addition, direct application of NE or activation of the LC efferent pathway modulates the response properties of thalamic (Rogawski and Aghajanian, 1980a,b; McCormick and Prince, 1988; McCormick, 1989) and cortical (Waterhouse and Woodward, 1980; Waterhouse et al., 1990; McLean and Waterhouse, 1994; Sessler et al., 1995; Manunta and Edeline, 1997; Waterhouse et al., 1998; Snow et al., 1999) sensory neurons. Finally, as reviewed above, ADHD patients are easily distracted by extraneous environmental stimuli suggesting a dysfunction in sensory signal processing. Thus, a strong link exists between the putative role of the LC-NE system in brain function, MPH actions and at least some of the behavioral symptoms associated with ADHD.

Modulatory Effects of NE on Single Neurons

Over the years, one of the major issues relating to the function of the LC efferent system has been elucidation of the cellular actions of NE in noradrenergic target areas of the brain. In the late 1970s, pioneering studies in monkey auditory cortex (Foote et al., 1975) demonstrated a differential depressant effect of

microiontophoretically applied NE on single neurons such that the spontaneous firing rate of recorded cells was suppressed to a greater extent than stimulus evoked discharges, thus yielding a net increase in "signal to noise" ratio. This initial study prompted many other laboratories to investigate the actions of NE in a variety of sensory circuits within the mammalian brain including olfactory bulb (Collins et al., 1984; Ciombor et al., 1999), dorsal lateral geniculate nucleus (Rogawski and Aghajanian, 1980a,b), visual, auditory and somatosensory cortices (Waterhouse and Woodward, 1980; Kasamatsu and Heggelund, 1982; Videen et al., 1984; Manunta and Edeline, 1997), and superior colliculus (Sato and Kayama, 1983; Mooney et al., 1990). In many cases, local application of NE was found to enhance responses of individual sensory neurons to synaptic stimuli (Rogawski and Aghajanian, 1980a,b; Collins et al., 1984; Ciombor et al., 1999); however, mixed effects were observed in other studies with suppression of stimulus-evoked discharge often predominating (Videen et al., 1984; Mooney et al., 1990; Manunta and Edeline, 1997). Thus, while there is general agreement that NE can modulate the responses of cells to non-monoaminergic synaptic inputs, the exact nature of that modulation and the conditions under which it can be observed in behaving animals are still open to question.

An in-depth analysis of the net facilitating effect of NE on synaptic transmission in the rat primary somatosensory cortex was carried out by Waterhouse and colleagues (Waterhouse et al., 1980; Waterhouse and Woodward, 1980; Waterhouse et al., 1981; Waterhouse et al., 1982) with the intent of characterizing the nature of this noradrenergic action at levels of iontophoretically released NE that had minimal or no effect on spontaneous discharge. Under these conditions, numerous instances were reported where stimulus evoked patterns of cortical cell discharge were increased well above control (Waterhouse et al., 1980; Waterhouse and Woodward, 1980). In other cases, local administration of NE revealed robust cellular responses to otherwise subthreshold synaptic stimuli (Waterhouse et al., 1988). These findings in cerebral cortex support the idea that a prominent physiological function of central noradrenergic pathways is to enhance the efficacy of both excitatory and inhibitory synaptic transmission within target neuronal circuits rather than directly suppress cell firing (Woodward et al., 1979). Later work in cat (Kasamatsu and Heggelund, 1982; McLean and Waterhouse, 1994) and rat (Waterhouse et al., 1990) primary visual cortex showed that NE can alter specific receptive field properties (e.g., direction selectivity, velocity tuning) of visually responsive cells. As such these results go beyond the demonstration of simple monoamine-induced changes in the magnitude of synaptically evoked responses and show that such actions can lead to selective alteration of the feature extraction properties of individual sensory neurons. Despite these advances, our knowledge of the cellular and circuit level actions of NE in cognitive regions of the brain is still quite limited.

A Role for the NE System in State Dependent Changes in Sensory Signal Processing

One of the unique emergent properties of the central nervous system is its ability to extract highly detailed information from the sensory surround. However, in order for an organism to make efficient and appropriate use of the continuous stream of incoming information, it must be able to regulate the sensitivity of this process as well as focus on that fraction of sensory input that is novel or relevant to an ongoing task. Such regulation of sensory processing capabilities represents the essence of an organism's ability to respond and adapt to changing environmental conditions and behavioral contingencies (Kahneman, 1973). Although evidence for state dependent regulation of sensory signal processing is abundant (Evarts, 1960; Steriade et al., 1969; Pfingst et al., 1977; Hyvarinen et al., 1980; Bushnell et al., 1981; Goldberg and Bushnell, 1981; Mountcastle et al., 1981; Steriade, 1990), neither the cellular basis nor the circuit mechanisms responsible for this dimension of CNS function has been elucidated. Nevertheless, evidence accumulated over the past 35 years suggests a fundamental role for the LC-NE system in maintaining behavioral and EEG indices of arousal and regulating sensory signal processing. A recent survey of anatomical, electrophysiological, and behavioral evidence has led to the hypothesis that the LC and possibly other noradrenergic pathways serve at least two general behavioral functions (Berridge and Waterhouse, 2003). First, these systems contribute to the induction of forebrain neuronal and behavioral activity states appropriate for the acquisition of sensory information (e.g., waking). Second, within the waking behavioral state, NE release enhances signal transmission and sensory information processing. Thus, the working hypothesis is that the LC-NE system is part of the neuronal machinery that regulates the efficiency of signal processing in brain circuits during different phases of arousal and sustained attention. Although this idea is attractive, it is well to remember that it is based for the most part on work done in sensory systems and has yet to be established for LC-noradrenergically innervated, cognitive networks such as those in the PFC.

Catecholamines have an Essential Influence on PFC Functions

It is now widely accepted that both NE and DA are necessary for normal PFC cognitive function. Many studies have suggested that either too little (Sawaguchi and Goldman-Rakic, 1994) or too much (Zahrt et al., 1997) D1 receptor stimulation impairs PFC function (Arnsten and Goldman-Rakic, 1998; Granon et al., 2000). Low doses of D1 agonists improve PFC function (Sawaguchi et al., 1988; Cai and Arnsten, 1997; Granon et al., 2000), while high levels of DA impair PFC function (Williams and Goldman-Rakic, 1995; Murphy et al., 1996), forming an "inverted U" curve of performance (Williams and Castner, 2006; Vijayraghavan et al., 2007). NE also has marked effects on PFC function, especially in the context of attention (Morilak et al., 2005; Miner et al., 2006). These actions may be particularly relevant to ADHD. As with DA, low to moderate levels of NE contribute to improved PFC function, whereas high concentrations of NE seem to impair PFC function, exhibiting a similar inverted-U relationship between LC-NE activity and optimal performance for attention tasks (Berridge and Waterhouse, 2003; Aston-Jones and Cohen, 2005). Modulation of PFC function by NE may involve α-2A receptors (Arnsten et al., 1988; Tanila et al., 1996; Jakala et al.,

1999; Li et al., 1999; Franowicz et al., 2002; Wang et al., 2007) or α-1 receptors (Lapiz and Morilak, 2006).

Both NE and DA systems are necessary for proper operation of prefrontal functions, since selective impairment of either NE or DA transmission in the PFC disrupts working memory (Brozoski et al., 1979). In fact, intact prefrontal cortical NE transmission is necessary for DA release, indicating the two systems are inseparable for normal operation of prefrontal functions (Ventura et al., 2003; Ventura et al., 2005; Ventura et al., 2007). Other studies indicate that complementary levels of catecholamine receptor stimulation are needed to optimize the operations of PFC circuits (Arnsten and Li, 2005; Pascucci et al., 2007). Although the results of these investigations emphasize the balancing roles of the NE and DA systems in normal PFC function and treatment of disorders involving PFC dysfunction, the precise mechanisms through which these effects occur have not been fully elucidated. Moreover, the question of how NE and DA might interact on cells and circuits in catecholaminergic terminal fields under normal conditions or conditions subsequent to psychostimulant administration has not been addressed.

In Contrast to DA, Noradrenergic Modulation of Synaptic Transmission in PFC Circuitry has been Relatively Neglected

Because of the critical role of the DA system in cognitive and motivational functions of PFC, DA regulation of cortical synaptic activity has been extensively studied. In PFC slices, DA decreases AMPA receptor-mediated EPSP/Cs via D1-mediated presynaptic mechanisms (Law-Tho et al., 1994; Gao et al., 2001; Seamans et al., 2001a). Although most studies show a decrease in the evoked AMPA EPSP/Cs by DA, two studies reported an increase in EPSP/Cs (Gonzalez-Islas and Hablitz, 2003; Onn et al., 2006). The reason for these contradictory results remains unclear, but one suggestion is that the effects of D1 receptors on PFC neurons are input-specific (Urban et al., 2002) or synapse specific (Gao and Goldman-Rakic, 2003).

DA regulation of inhibition in the PFC appears more complicated. It seems that DA differentially modulates spontaneous (Penit-Soria et al., 1987) and evoked IPSPs (Law-Tho et al., 1994), in spite of the fact that both are largely dependent on action-potential mediated release of GABA, and hence, should theoretically share common presynaptic release machineries (Zhou and Hablitz, 1999; Gonzalez-Islas and Hablitz, 2001; Seamans et al., 2001b; Gao et al., 2003; Kroner et al., 2007). In addition, DA exhibited a biphasic modulation of IPSPs, via combined D1 and D2 effects (Seamans et al., 2001b; Trantham-Davidson et al., 2004) or a D4-mediated postsynaptic modulation (Wang et al., 2002).

By comparison, adrenergic regulation of synaptic transmission in prefrontal circuits, especially cortical inhibition, has largely been neglected. Recording from layer 5 pyramidal neurons of rat sensorimotor cortex (Bennett et al., 1998) found that epinephrine had mixed effects on evoked IPSCs, with depression more commonly observed. In agreement, Kawaguchi and Shindou (1998) also reported either excitatory or inhibitory adrenergic effects on identified GABAergic interneurons, depending on cell type. Waterhouse and colleagues demonstrated prominent noradrenergic potentiating effects on GABA-mediated inhibition in layer V somatosensory cortical pyramidal neurons (Sessler et al., 1995) and cerebellar Purkinje neurons (Sessler et al., 1989) that were mediated by β receptor linked cAMP mechanisms. Waterhouse et al. (2000) further showed a differential NE modulation of synaptic excitation in regular spiking (increase) and intrinsic bursting (decrease) layer 5 pyramidal neurons of somatosensory cortex; these actions appear to be mediated by α-1 and β receptors, respectively (Devilbiss and Waterhouse, 2000). Despite these findings, there has not been a full accounting of how NE regulates synaptic communication in individual pyramidal neurons and interneurons in PFC circuitry.

Cellular Actions of NE in PFC

Because *in vivo* study of inhibitory circuitry is difficult, *in vitro* paired or quadruple recordings are particularly advantageous for the exploration of the monosynaptic connections between or among individual identified neurons. We have used this approach to study dopaminergic modulation of recurrent excitation and inhibition (Gao et al., 2001; Gao and Goldman-Rakic, 2003; Gao et al., 2003) and NMDAR-mediated currents in recurrent excitation (Wang et al., 2008) in prefrontal cortical circuits. This unique approach allows us to distinguish unambiguously the drug effects on different types of synaptic connections, which are unattainable using other techniques. To measure the postsynaptic currents in monosynaptic connections between individual identified neurons, we employed multiple patch-clamp recordings in prefrontal neurons. Whole-cell patch clamp recordings were conducted in prefrontal cortical slices through an upright microscope (Olympus BX61, Olympus Optics, Japan) equipped with infrared-differential interference contrast optics (IR-DIC) and a digital video camera. A key issue for studies in cortical slices is the ability to distinguish cells as interneurons or pyramidal neurons. In the past decade, we have employed this technique to successfully identify the recorded neurons (Gao et al., 2001; Gao and Goldman-Rakic, 2003; Gao et al., 2003; Gao, 2007; Wang and Gao, 2009, 2010). All neurons were initially identified by their morphologies under infra-red video microscopic visualization. Pyramidal neurons (P) are large cells with triangular soma and pia-oriented apical dendrites; the fast-spiking GABAergic interneurons (NP) are small cells with multipolar dendrites and round or oval cell bodies. The identities of these neurons are confirmed by their physiological properties and biocytin-labeled morphologies (Fig. 1). In P, injection of depolarizing current pulses evokes a train of long-duration (half-width ~1.2 ms) spikes with profound adaptation followed by a weak fast after hyperpolarization (fAHP ~2–3 mV). In contrast, NP fires short duration (half-width ~0.5 ms) high frequency spikes with no adaptation and a significantly stronger fAHP (~13 mV). In addition, the spike amplitude of P is also significantly larger (~80 mV) than that of NP (~60 mV) (Gao, 2007).

Ongoing studies (Sessler, 2008) have focused on the effects of NE application on excitability and synaptic transmission in PFC slices. Figure 2 illustrates the influence of NE (10 μM) on both presynaptic and postsynaptic cells in a reciprocally connected P-NP pair. The resting potentials of both cells were depolarized by NE

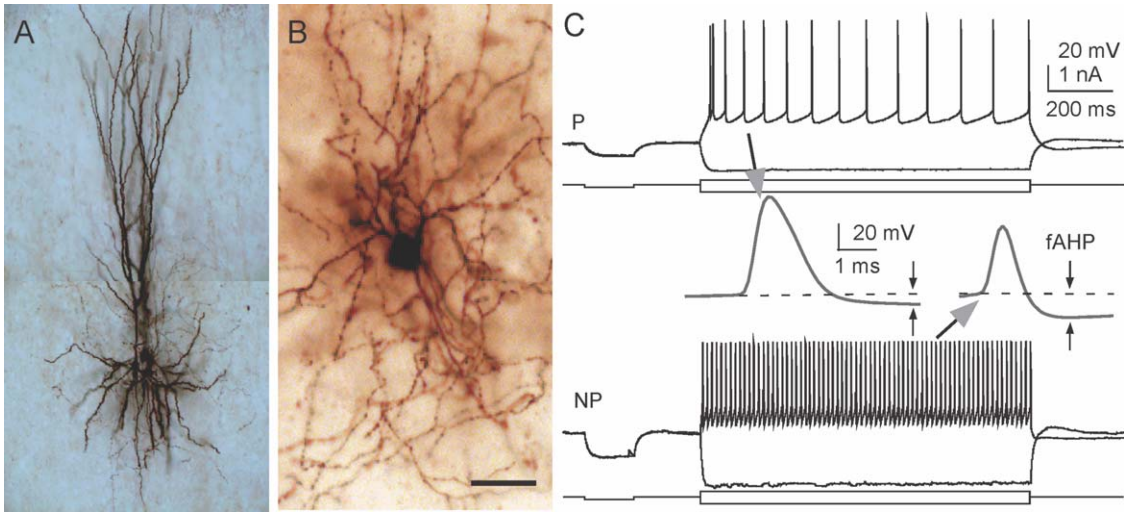

Fig. 1. Morphological characteristics and firing patterns of pyramidal cells (P) and a fast-spiking interneuron (NP). **A** and **B**: Biocytin-labeled P (A) and a multipolar NP, which has clear multiple dendritic processes with characteristics of basket cells (B). Scale bar = 100 μm for A and 50 μm for B. **C**: Current-clamp recordings from one of the four simultaneously recorded P (top) and the NP (bottom). The middle insets show single spikes on an expanded time scale. Before step currents, a negative current (0.1 nA) was applied to monitor the input resistance of the recorded cells. Note the wide action potential, low firing rate, prominent firing adaptation, and small fAHP in P. In contrast, the NP has a narrower action potential, higher firing rate without adaptation, and a larger fAHP. Reproduced from Gao 2007, J Neurophysiol, with permission from the Am Physiol Soc.

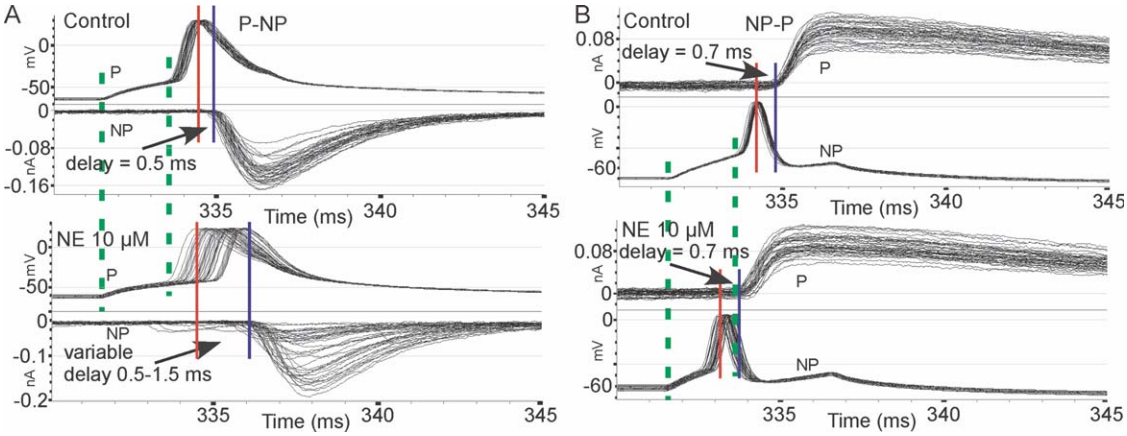

Fig. 2. NE depolarizes both P and NP, but seems to affect P much more strongly than NP in this reciprocally connected pair. **A**: Action potentials were evoked by intracellular current injection in P and the EPSCs (40 sweeps) were recorded in NP. The delays of EPSCs were determined from the peak of action potentials (red lines) to the onset of the EPSCs (blue lines). The bath application of NE caused significant spike delay in P and clear synaptic failure and EPSC reduction in NP. **B**: The action potentials were evoked in NP whereas the IPSCs were recorded in P. NE depolarized the NP yet caused spike advances, and had a relatively small effect on IPSCs.

(lower parts of A and B). Surprisingly, evoked spikes in P (Fig. 2A) were delayed in onset (green dashed lines) and appeared to have slightly lower amplitudes when NE was applied to the bath (Fig. 2A, bottom) than they had during control conditions. In contrast, spikes evoked in NP (Fig. 2B) appeared slightly earlier, but their amplitude seemed to be unchanged. This demonstrates a differential presynaptic effect of NE on P versus NP. NE effects on postsynaptic currents also show a difference between P and NP in this pair. The P-NP EPSC was both delayed and reduced (Fig. 2A, bottom) compared to control, and synaptic failures were evident. In contrast, the NP-P IPSC (Fig. 2B) appeared to be unaffected by NE. The mechanism underlying this pronounced differential effect of NE on postsynaptic currents in P versus NP may involve presynaptic and/or postsynaptic factors. In any event, the overall effect of NE appears to shift the balance between cortical excitation and inhibition in favor of inhibition, as the excitatory influence of P on NP is delayed and diminished, while the inhibitory influence of NP on P is relatively unaffected. Such effects likely have important consequences in terms of PFC circuit function under attentional load and in the presence of systemically administered psychostimulants.

Differential Modulation of P-NP Connections by NE and DA in the PFC

In a previous study, Gao and Goldman-Rakic (2003) demonstrated differential DA regulation of excitatory transmission between layer 5 P and NP in the ferret PFC (Gao and Goldman-Rakic, 2003). DA selectively depresses the EPSP in P-P recurrent excitation but has no clear effect on the EPSP in P-NP connections. This target-specific dopaminergic regulation is further supported by the immuno-EM finding of target-specific D1 receptor-immunoreactivity on axonal terminals in the PFC (Paspalas and Goldman-Rakic, 2005). The absence of a DA influence on P-NP synapses has been confirmed in our recent preliminary study ($N = 5$) in the rat mPFC as well as demonstration of differential effects of DA and NE on P-NP connections: DA (10 μM) has no effect on the EPSC, just as we found in ferret PFC (Gao and Goldman-Rakic, 2003) whereas NE consistently depressed it (from Sessler, 2008). This difference in effect of NE and DA on P-NP excitatory transmission is extremely interesting because the reverse (DA depresses, NE has no effect) is observed on IPSCs in NP-P connections (Gao et al., 2003). The different modulatory effects of NE and DA on prefrontal synapses *in vitro* are also in agreement with a previous *in vivo* study in which NE and DA were found to have different modulatory effects (DA increases while NE decreases) on the neuronal activity related to a delay response task in the behaving monkey PFC (Sawaguchi et al., 1990). At this point, additional studies are needed to elucidate the underlying mechanisms and to consider the net impact of simultaneous exposure of PFC neurons to NE and DA, that is, as would occur after MPH. Answers to such questions are critical to understanding how MPH influences PFC function in intact animals and ADHD patients.

Interactions of Catecholaminergic Transmitters in PFC

As discussed above, NE and DA individually provide critical modulatory influences on prefrontal functions (Mingote et al., 2004; Arnsten and Li, 2005; Aston-Jones and Cohen, 2005; Morilak et al., 2005; Rossetti and Carboni, 2005; Drouin et al., 2006). Furthermore, there is evidence of interdependence of these transmitters. For example, intact prefrontal cortical NE transmission is essential for the motivational salience function of the DA-cortical pathway (Ventura et al., 2003). It is likely that the balance between excitatory and inhibitory circuitry in the PFC is dynamically adjusted in the waking animal by synergistic (or antagonistic) regulatory actions of NE and DA. Because MPH treatment alters the levels of both NE and DA, it is essential that we consider not only the actions of the individual transmitters on target neurons, but also their interactions and combined effects to understand the effects of this class of drug on PFC function during vigilance and enhanced cognition.

BEHAVIORAL MEASURES OF ATTENTION

Sustained Attention

Sustained attention is operationally defined as a behavioral state of vigilance that often occurs when an organism is presented with unpredictable, yet relevant, stimuli. This mode of attention has been viewed from a wide range of perspectives including human performance, cognitive neuroscience and pharmacology. Clearly, from a neuroethological point of view, regulation of vigilance is a key element in the defensive strategies of predatory-prey encounters. Although well-studied networks exist to coordinate predator avoidance in response to an imminent attack (DiDomenico et al., 1988; Eaton et al., 1988; Nissanov, 1989; Nissanov et al., 1990; Eaton et al., 1991), vigilance serves as a much earlier line of defense.

Signal length, the duration of intervals between presentations, order of signal presentations, signal intensity, and signal modality have all been shown to contribute to an animal's attentional performance. Sarter's group (McGaughy and Sarter, 1995) has developed and validated a behavioral procedure incorporating these factors to assess vigilance in a rat model. The paradigm, which we have modified for use in ongoing studies, consists of serial presentation of signal (S) and nonsignal (NS) events. The signal is a brief illumination of a stimulus light. In response to presentation of S, animals are trained to press one of two levers. The other lever is to be pressed when a NS event occurs. The order of S and NS presentation is random with equal probability of either one on a particular trial. The serial presentation of stimuli in this task is more demanding and better taxes attentional capabilities (Parasuraman, 1987) than older assays which called for simultaneous discrimination between signal and background (e.g., Stephens, 1988).

A key aspect of sustained attention is the inability of the animal to predict the timing of the stimulus (Parasuraman, 1987). In this behavioral procedure, the intertrial interval (ITI) is made variable. Thus, a stimulus may occur any time over the duration of a stimulus window or, in a NS trial, the stimulus light remains un-illuminated during the entire duration. Immediately after the S or NS event occurs, the response bars are extended for a brief time period before being retracted. Thus, for all trials the time from stimulus to response is short and is equivalent from trial to trial; any working memory aspects to the task are unchanged from trial-to-trial. Correct responses, both correct detection of S trials (hits) and correct rejection in NS trials, are immediately rewarded.

Impact of MPH on Sustained Attention

Sustained attention tasks have significant utility in experimental strategies designed to examine the impact of psychoactive drugs on specific dimensions of cognitive performance or to evaluate the outcome of genetic, chemical, or electrolytic CNS lesions. To demonstrate that our task required high attention for successful performance, we varied stimulus presentation time while matching all other aspects of the task such as reward frequency, stimulus environment, response rules and memory requirements. We reasoned that if the stimulus time could be predicted, the demand on the system would be reduced. Accordingly, our "low attention" protocol consisted of a short duration (15 msec) S or NS that always occurred at 7.5 sec after the start of a trial, and our "high attention" protocol consisted of the same visual signal or

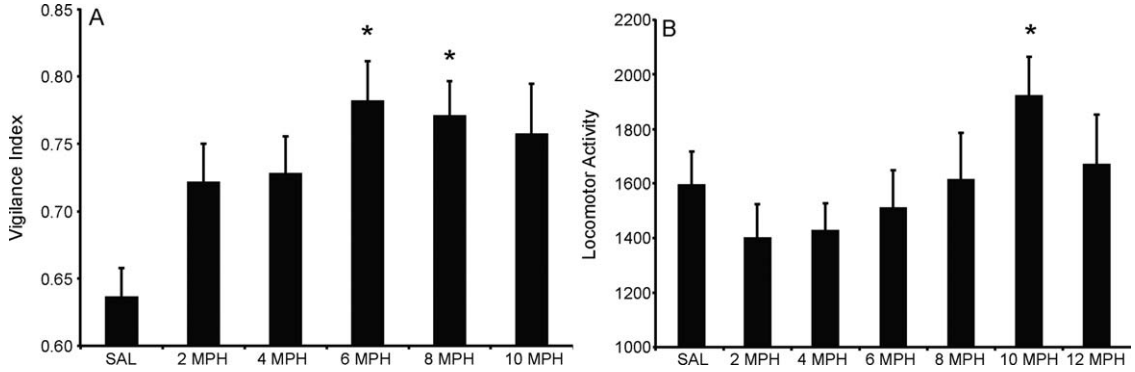

Fig. 3. Effects of oral MPH administration on sustained attention and locomotor activity. **A** and **B**: Male SD rats (N = 11) were trained to stable baseline performance (VI > 0.35) and given oral doses of MPH 20 min before the behavioral task with at least a 24 hr washout period between doses. Oral doses of 6.0 and 8.0 mg/kg MPH significantly enhanced vigilance index, separable from the dose of 10 mg/kg, which enhanced locomotor activity (measured by photobeam crossings in a 3 × 3′ locomotor chamber). (*$P < 0.05$). The dose of 12 MPH produced sedative side effects that interfered with data collection in the sustained attention task.

nonsignal that was randomly presented within a 15 sec window. Response levers were extended immediately following S or NS under both conditions. Rats were trained to stable performance on both the low and high attentional versions of this procedure and were then shifted to the opposite condition. Our hypotheses were that normal male rats trained on the high attention condition would continue to perform well under the low attention condition, and that rats trained on the low attention condition would perform poorly on S trials but not on NS trials under high attention conditions. This hypothesis was fully supported by our results, confirming that this procedure is able to dissociate attentional components of performance (Shumsky, 2000).

Next, we examined whether this attentional model was sensitive to MPH (Shumsky, 2004). Relative performance was assessed using changes in vigilance index (VI; McGaughy and Sarter, 1995), a combined measure computed from the numbers of correct and incorrect responses in both S and NS trials. VI can range from −1 to 1, with a value of 0 indicating 50% correct choices (consistent with chance), and +1 indicating 100% correct choices in both S and NS trials. Male SD rats trained under high attentional load conditions of the task (N = 6) displayed a significant increase in VI (*$P < 0.05$) 10–55 min after acute MPH (2.0 mg/kg IP) administration (Fig. 3A). These effects were most prominent in rats with the lowest vigilance baseline performance, suggesting that the least attentive animals received the most benefit from the drug when required to perform under high attentional load (data not shown). These results demonstrate that acute, low dose MPH administration can improve visual sustained attention in normal rats. A separate locomotor test demonstrated that MPH only increased activity at higher doses (5 mg/kg;*$P < 0.05$) and did not affect activity at the dose (2.0 mg/kg) that enhanced attention. We have found similar results using oral MPH administration (Shumsky, 2009) in which doses of 6.0 and 8.0 mg/kg significantly enhanced vigilance performance (Fig. 3A) while a dose of 10.0 mg/kg enhanced locomotor activity in the same animals (Fig. 3B). This shift in the dose response curves is consistent with first pass effects. These latter findings indicate that oral drug administration, the mode of drug delivery that most closely approximates human conditions, is suitable for animal studies.

Effects of Chronic MPH on Sustained Attention

We have also tested the effects of chronic, low dose MPH on acquisition of this sustained attention task under high attentional load in normal male SD rats (data not shown). After a training phase, rats were given daily ip injections of either 2.0 mg/kg MPH (N = 7) or saline (N = 8). MPH treated rats showed faster acquisition (a shorter number of trials to reach criterion performance) and better performance (greater VI at plateau) than saline controls. Once MPH treatment was withdrawn, VI dropped within 24 hr to a level equal to that of the saline control group, without increased reacquisition. A subsequent MPH dose response curve performed on these animals was no different from that obtained with saline controls. Thus, no tolerance was observed under these conditions and the ability of MPH to increase sustained attention accounts for its enhancement of task acquisition, suggesting that its behavioral impact is on attentional processing rather than on learning (Smith, 2005).

ELECTROPHYSIOLOGICAL INDICES OF MPH ACTION IN PFC

In addition to behavioral investigations, an increasing number of studies combine behavioral paradigms with extracellular recording procedures in specified brain regions to establish relationships between cellular discharge properties, neural circuit operations, and performance outcomes. In recent studies, we have begun to characterize the impact of low dose MPH on performance in the sensory guided sustained attention task and then, using multi-channel, multi-neuron recording procedures established links between spike train activity of PFC neurons, task performance, and drug actions. A major advantage of this approach is the opportunity to study the electrophysiological actions of MPH on large arrays of neurons recorded simultaneously and across a dose range that: (1) promotes release of NE and DA in catecholamine terminal fields (Kuczenski and Segal,

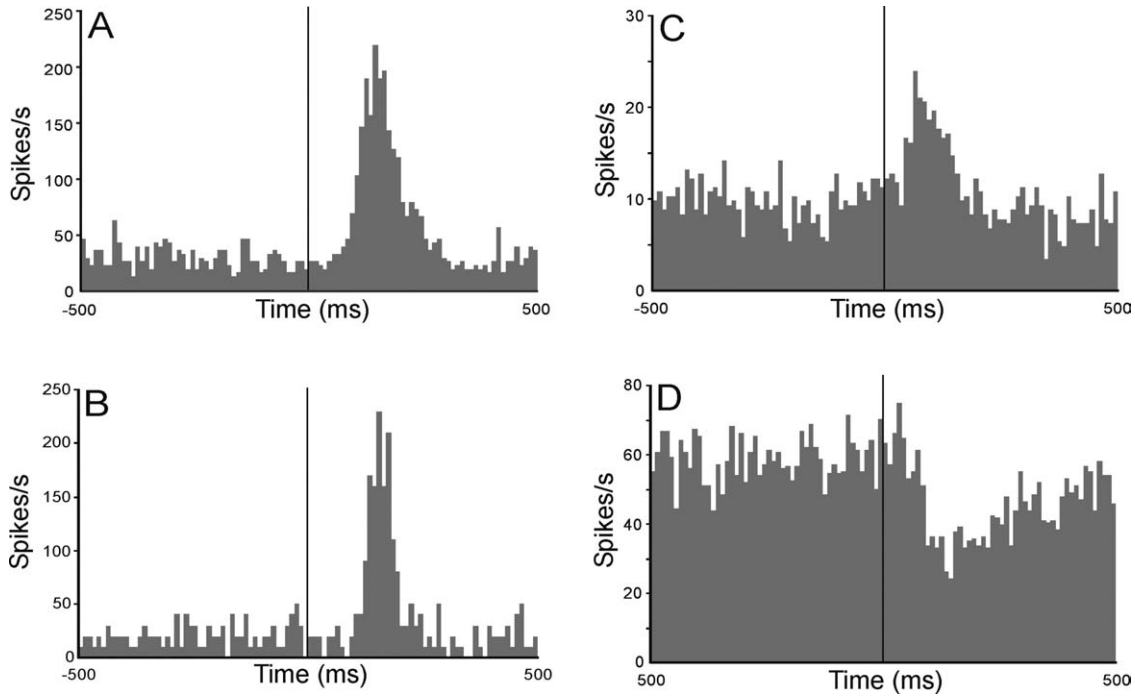

Fig. 4. Peri-stimulus time histograms showing responses of PFC neurons to cues during the task. **A** and **B**: A single neuron that showed an earlier and more robust response to light flash when the subsequent response was a Hit (A) than when it was a Miss (B). **C** and **D**: Two different neurons showing opposite responses (C, excitation; D, inhibition) to lever presentation.

2002), (2) produces measurable changes in animal performance on a sustained attention task ((Shumsky, 2004), and (3) is clinically relevant (appropriate plasma levels) for ADHD treatment (Berridge et al., 2006).

In preliminary studies (Clark, 2008), we have recorded spike train activity from ensembles of single neurons in the medial PFC while the animal performed the sustained attention task described above. Rats previously trained to criterion performance were surgically implanted with bundles of 8 microwires, allowed to recover, and re-trained to perform the task with an attached head stage and amplifier cable. Our initial goal has been to catalog patterns of neuronal behavior while the animals were engaged in the task, and to investigate whether any features of neuron firing were associated with greater or lesser levels of vigilance within a session, as assessed by performance (i.e., assuming that on average, correct responses were associated with greater vigilance, and incorrect responses or omissions were associated with lesser vigilance). We have found several cases of neurons changing their firing rates in association with sensory (Fig. 4) or motor (Fig. 5) events. Figure 4 illustrates several features of sensory responses. First, there are cells that respond to the light cue (A and B), or the lever presentation (C and D). Second, firing rates may increase (A–C) or decrease transiently (D) in response to the stimulus. Finally, neurons that respond to sensory events show differences associated with subsequent performance. For example, the cell in Fig. 4A,B, exhibited a response to the light cue that was broader, and had shorter latency for "Hit" trials (A) than for "Miss" trials (B) or omissions (not shown). Neurons that show changes in firing in conjunction with lever pressing often show increases prior to pressing the ipsilateral lever (Fig. 5A vs. C), but occasionally the contralateral lever (Fig. 5B vs. D) or both (not shown). Overall, these results suggest a prominent relationship between behavioral state (vigilance/correct performance) and PFC neuronal responsiveness to task related events.

A second goal has been to compare measures of neuronal activity following MPH (2 mg/kg, IP) or saline injection. In many cases, we have recorded from well-isolated cells on multiple successive days, administering either saline or MPH prior to behavioral testing on a given day. In other cases, we have broken a single 45 min experimental session into halves, administering saline 10 min before the first session (22.5 min), and either saline or MPH 10 min before the second session (22.5 min). In some instances, we have observed neurons that discharge faster when MPH is present, (Fig. 6 solid bars vs. open bars), but other cases where MPH decreases tonic firing rate. We are working to understand these effects, which may be related to variation among rats with respect to MPH-induced changes in overall activity. A further observation is shown in Fig. 7, where a single neuron exhibited a high basal firing and minimal response to the cue light for Hit trials after saline injection (Fig. 7A) but a reduced background discharge and a robust cue light response after MPH injection (Fig. 7B). The net outcome of these changes is a dramatically increased signal to noise ratio following MPH administration.

Overall, these preliminary findings suggest prominent behavioral state and psychostimulant drug-dependent influences on task related discharge of individual PFC neurons. The trend is toward enhanced neuronal

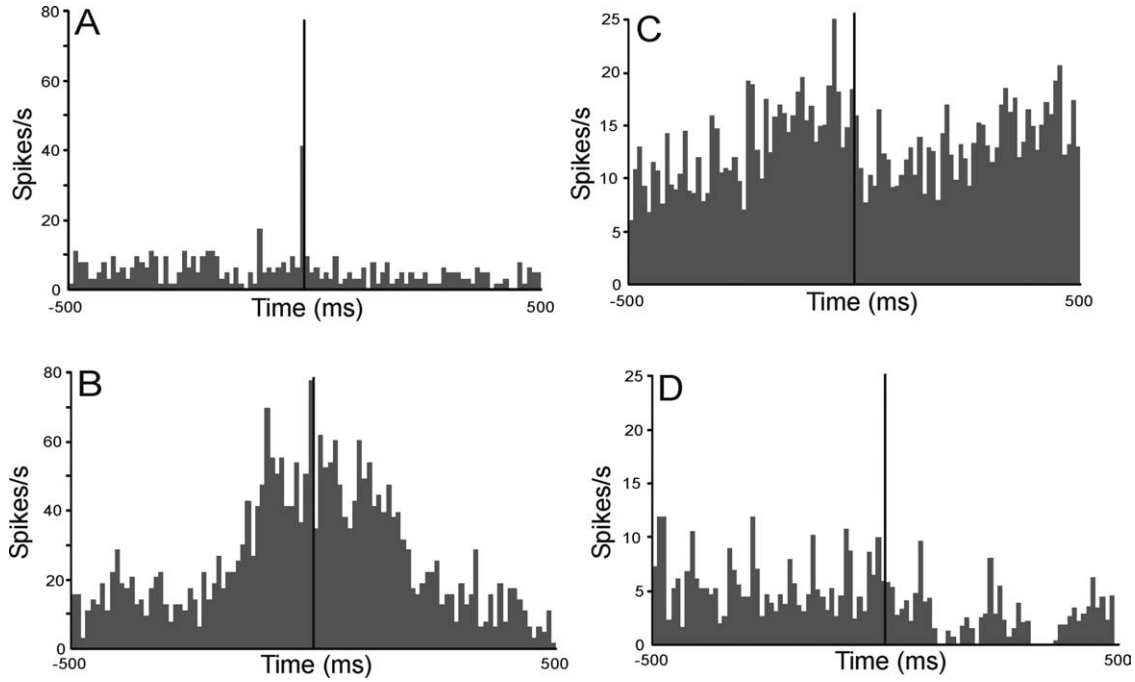

Fig. 5. Motor correlates of PFC unit discharge. Peri-event histograms illustrate responses of two neurons recorded from the left PFC with respect to lever pressing ($t = 0$). **A** and **C**: A cell with negligible activity associated with Left lever press, but an increase in activity centered on Right lever press. **B** and **D**: A second cell with activity increasing before Left lever press, but much lower activity associated with Right lever press.

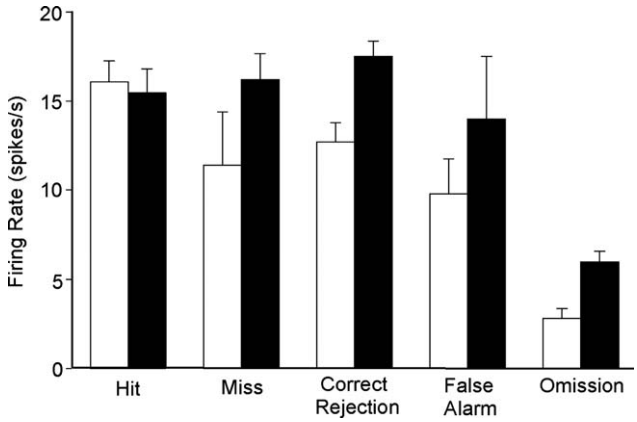

Fig. 6. Firing rate of a single PFC neuron during performance of the sustained attention task, divided by trial outcome, that is, correct responses ("Hit" and "Correct Rejection"), incorrect responses ("Miss" and "False Alarm"), and Omissions. Firing rate is shown for 1 sec before lever presentation, shown for White bars: Saline. Black bars: MPH (2 mg/kg). Error bars: +1 SEM.

responsiveness during periods of good performance (vigilance) or following MPH administration. Thus, MPH promotes conditions in the PFC of rat brain that mimic those observed during periods of vigilance.

SUMMARY

MPH is used effectively in low dose, long-term regimens to treat ADHD in children, adolescents, and adults. The net impact of MPH administration is increased NE and DA neurotransmission throughout the brain. Although the biochemical mechanisms responsible for this effect are well known, the conceptual framework for understanding the physiological basis of MPH efficacy in ADHD treatment or its ability to improve cognitive function in normal individuals is lacking. In this context, there have been major advances in our understanding of the cellular/membrane actions of NE and DA on target neurons in the brain, yet we still do not fully comprehend how output from noradrenergic and dopaminergic pathways regulates cellular function, neural circuit operations, and cognitive processes in intact animals. Systemic administration of MPH is a valuable tool for addressing these issues. Furthermore, a major gap in our understanding of ADHD neuropathology is a thorough understanding of the physiological mechanisms that mediate MPH efficacy in ADHD treatment. Previous studies of psychostimulant drug action in general, and MPH action, in particular, have relied upon dosing regimens that mimic drug abuse/drug addiction conditions rather than low dose regimens that mirror therapeutic management of ADHD patients. Moreover, behavioral and electrophysiological studies of psychostimulant drug action are often conducted independent of one another, thus creating a "disconnect" between physiological mechanisms and behavioral outcome.

PROPOSED COMPREHENSIVE EXPERIMENTAL ANALYSIS OF MPH ACTIONS

With the above considerations in mind, we propose the following comprehensive strategy to further elucidate

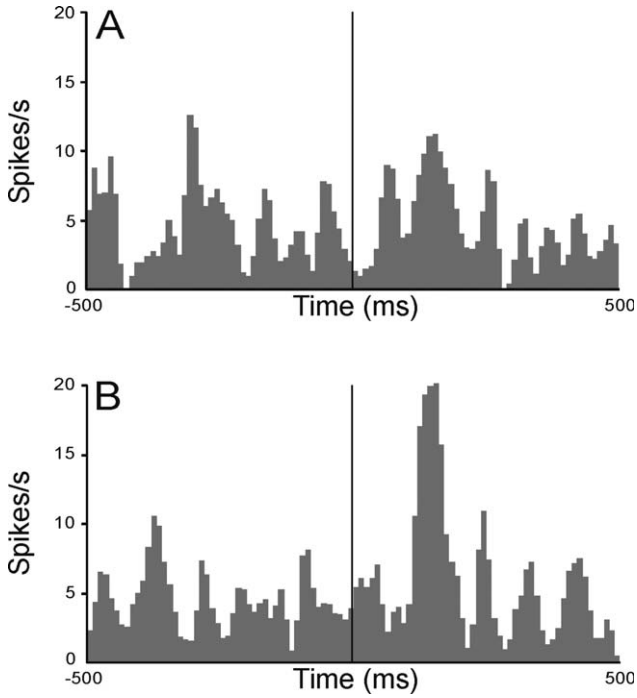

Fig. 7. Peri-stimulus time histograms illustrating cue-evoked responses of a single PFC neuron during Hit trials. **A**: Following saline injection. **B**: Following MPH injection, 2.0 mg/kg i.p.

the actions of MPH as they pertain to treatment of attention disorders. First, employ pharmacologic approaches to assess the contributions of specific catecholaminergic systems to the improvement in animal performance caused by low-dose MPH in well characterized behavioral tasks such as attention set shifting and sensory-guided sustained attention. Second, examine the effects of the same low-dose MPH administration on the task related discharge of prefrontal cortical neurons. The purpose of this work is to identify the parameters of PFC neuronal function that are subject to regulation by psychostimulant drugs and task-related behavioral state. Third, use whole cell recording techniques to examine the actions of NE and NE + DA on membrane response properties and synaptic transmission in identified subsets of PFC neurons. The goal of these studies is to define the individual and combined actions of catecholamine transmitters on PFC neuron physiology and then to use this information to predict how MPH-induced increases in extracellular DA and NE affect cellular and circuit functions of the PFC. In this regard, computational models of the PFC based upon data from cellular investigations would be useful in identifying the parameters of neuronal function that are not only critical to PFC operations but also are subject to regulation by psychostimulant drug actions. Fourth, examine the impact of MPH on models of executive function in adolescent and juvenile animals as these are the age brackets when psychostimulant treatment of ADHD is most prevalent. Fifth, extend all of the preceding studies to well-established animal models of ADHD.

Drug effects should be correlated across all levels of investigation establish an overarching explanation of how MPH impacts PFC operations from cellular through behavioral functional domains. In all of these studies, routes of administration, dosages, and dosing schedules (i.e., weekday treatment vs. weekend drug "vacation") should be carefully selected so as to as to mimic as closely as possible clinical and off-label usage of MPH for ADHD and cognitive enhancing applications, respectively. Finally, both acute and chronic regimens of drug treatment should be examined in order to identify both immediate and persistent effects of psychostimulant therapy. An additional strategy involves assessment of behavioral capabilities and physiological measures in adult animals after receiving chronic drug treatment as juveniles and adolescents.

FINAL CONSIDERATIONS

Although any of the amphetamine-like stimulants could be examined using the proposed strategy, MPH is under initial consideration because it is the most widely prescribed and therefore the prototypic ADHD medication. Moreover, when used at low doses and in moderation, MPH can enhance attention, improve concentration, and promote clarity of thought in otherwise normal individuals. Mounting evidence indicates increasing off-label and illicit use of MPH and other psychostimulant drugs for cognitive enhancement. Teenagers, young, and middle aged adults, and elderly citizens are turning to psychostimulants as a means of improving mental performance (Farah et al., 2004; Guardian, 2007; Greely et al., 2008). Collectively, these observations suggest that a systematic investigation of the behavioral and physiological actions of low-dose MPH in intact animal preparations will reveal new insights regarding the neural systems and circuit operations responsible for sustained attention and ADHD pathology. Furthermore, *in vitro* examination of NE and DA effects in PFC will reveal cellular and synaptic actions of the endogenous transmitters that underlie MPH effects on vigilance and cognitive function. Although it is possible that normal mechanisms of vigilance and clinical manifestations of ADHD are unrelated, the proposed experimental plan will, at minimum, provide detailed information that can serve as a basis in future studies for distinguishing between these two conditions. We also believe that an important by-product of such studies will be the development of a sophisticated set of assays for screening new, safer ADHD drugs and for evaluating neural dysfunction in animal models of ADHD.

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