Methylphenidate Enhances Noradrenergic Transmission and Suppresses Mid- and Long-Latency Sensory Responses in the Primary Somatosensory Cortex of Awake Rats

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Drouin, Candice, Michelle Page, and Barry Waterhouse. Methylphenidate enhances noradrenergic transmission and suppresses mid- and long-latency sensory responses in the primary somatosensory cortex of awake rat. J Neurophysiol 96: 622–632, 2006. First published May 10, 2006; doi:10.1152/jn.01310.2005. Noradrenergic neurons send widespread projections to sensory networks throughout the brain and regulate sensory processing via norepinephrine (NE) release. As a catecholamine reuptake blocker, methylphenidate (MPH) is likely to interact with noradrenergic transmission and NE modulatory action on sensory systems. To characterize the neurochemical actions of MPH in the primary sensory cortex of freely behaving rats and their consequences on sensory processing, we measured extracellular NE levels in the primary somatosensory (SI) cortex by microdialysis and recorded basal and sensory-evoked discharge of SI cortical neurons. At 5 mg/kg, MPH significantly increased locomotor activity and induced a significant suppression of the short-latency excitation, which probably resulted from the MPH-induced change in behavior. In addition, both doses of MPH suppressed the postexcitatory inhibition and the long-latency excitation evoked by the stimulation of the whisker pad. These effects did not seem to result from the locomotor effect of MPH and probably involved MPH-induced enhancement of noradrenergic transmission.

INTRODUCTION

Considerable evidence suggests that norepinephrine (NE) plays an important role in arousal-dependent and attention-induced modulation of sensory signal processing (Berridge and Waterhouse 2003). Indeed, electrophysiological recordings of noradrenergic neurons in the locus coeruleus (LC) of rodents and primates have shown that these cells respond specifically to novel or meaningful sensory stimuli while their basal firing rate is regulated by the state of vigilance of the animal (Aston-Jones et al. 1991, 1994; Foote et al. 1980, 1991). Moreover, numerous studies have shown that application of NE (Devilbiss and Waterhouse 2000; George 1992; Manunta and Edeline 1997; Waterhouse et al. 1980, 2000) or activation of the LC (Devilbiss and Waterhouse 2004; Holdefer and Jacobs 1994; Lecas 2004; Snow et al. 1999; Waterhouse et al. 1998) can modulate the processing of incoming sensory information in primary sensory circuits of mammalian brain. Consistent with this view is the hypothesis that a dysfunction in noradrenergic transmission may be responsible for some of the symptoms (e.g., distractability and inattentiveness) observed in patients suffering from attention-deficit, hyperactivity disorder (ADHD). Indeed, psychostimulants prescribed for the treatment of ADHD, such as methylphenidate (MPH), enhance noradrenergic transmission by blocking NE reuptake via its transporter (Kuczenski and Segal 1997). Considering the well-established modulatory action of NE within sensory systems, we postulated that MPH administration would induce NE-mediated effects on sensory circuits, an action that may contribute to the therapeutic efficacy of MPH in the treatment of ADHD patients.

As a catecholamine reuptake inhibitor, MPH was found to increase extracellular levels of NE in the prefrontal cortex and the hippocampus (Bymaster et al. 2002; Kuczenski and Segal 2001; Marsteller et al. 2002). However, the impact of MPH varies across studies and brain regions. Moreover, it was never measured in sensory cortical areas. Therefore we first quantified the effect of MPH on extracellular levels of NE in the primary somatosensory (SI) cortex using microdialysis.

To characterize the neurophysiological actions of MPH on sensory systems, we then recorded basal and sensory-evoked discharge of SI cortical neurons in freely behaving rats before and after MPH administration using multi-channel recording techniques. We also quantified the locomotor activity of the animals during each recording session to characterize the behavioral effects of the doses of MPH used in our study. We focused our electrophysiological analysis on infragranular layers, which are considered the output layers of the SI cortex. Indeed, neurons in infragranular layers send projections back to the somatosensory pathways (Bourassa et al. 1995; Zhang and Deschenes 1997) as well as to brain areas implicated in ADHD, such as the prefrontal cortex (Golmayo et al. 2003) and the striatum (Hoffer and Alloway 2001; West 1998). Moreover, these cells receive inputs from all other layers of the SI cortex.
(Staiger et al. 2000), so that any influence of MPH along the ascending somatosensory pathway should impact their activity.

METHODS

Subjects

This study was performed on 17 male adult Long-Evans rats (Charles River, Boston, MA) weighing 225–250 g on arrival. After arrival animals were housed in the animal facility for ≥ 1 wk before surgical procedures. All procedures described below were approved by the Drexel University Institutional Animal Care and Use Committee and followed the National Institutes of Health guidelines.

Drugs

MPH (Sigma) was dissolved in saline (0.9%) at a concentration of 1 or 5 mg/ml. Saline and MPH solutions were administered intraperitoneally (ip) at 1 ml/kg.

Microdialysis studies

Each dose of MPH (1 and 5 mg/kg) was tested in a separate group of animals (n = 5 in each group).

PROBE IMPLANTATION AND SAMPLE COLLECTION. The microdialysis probe was surgically implanted in the SI cortex under sodium pentobarbital (17.5 mg/kg ip)/chloral hydrate 5% (400 mg/kg ip) anesthesia. During the surgery, three stainless steel screws were fixed to the skull to serve as anchors for cementing the probe in place with dental acrylic.

Vertical concentric microdialysis probes with a 2-mm active area (where exchange across the membrane occurs) and a 0.5-mm epoxy plug at the tip were built as previously described (Abercrombie et al. 1988; Page et al. 2004), using a semipermeable membrane of hollow regenerated cellulose fibers with a 280 μm OD and a 13,000 MW cutoff (SpectraPor, Spectrum, Houston, TX). The recovery rate of each probe was determined in vitro by placing the probe in a standard solution of NE in artificial cerebrospinal fluid (ACSF), and probes that did not correspond to a standard range of recovery (10–22%) were eliminated.

After a small craniotomy above the whisker representation of the SI cortex (2.5 mm posterior and 4.6 mm lateral to bregma) and incision of the dura, the microdialysis probe was slowly lowered at a 10° angle (the tip of the probe being more rostral) to a depth of 3 mm from dura into the SI cortex and secured with skull screws and dental acrylic. The inlet of the probe was connected to a fluid swivel (Instech Labs, Plymouth Meeting, PA), and the rat was placed into a clear Plexiglas circular cage (Instech Labs) with water and food available ad libitum. A P-200 dental acrylic.

The recording electrodes consisted of an array of eight blunt-tipped Teflon-coated stainless-steel wires (50 μm in diameter) aligned in the rostrocaudal axis and spaced 0.2 mm from one another (NBLabs, Dennison, TX). After a small craniotomy above the whisker representation of the SI cortex (1–3 mm posterior and 5 mm lateral to bregma) and incision of the dura, we slowly lowered the electrode array into the infragranular layers of the SI cortex. During this procedure, we recorded neural activity and determined the principal whisker for each electrode. This raw receptive field assessment confirmed the position of the electrode array (Fig. 1C) and allowed us to target the appropriate area of the whisker pad with the stimulating electrode.

The whisker-pad electrode, which consisted of a twisted pair of seven-stranded stainless-steel Teflon-coated wires (No. 793200; A-M Systems, Carlsborg, WA) connected to an MS303-120 connector (Plastics One, Roanoke, VA), was placed subcutaneously within the rat whisker pad (Devilbiss and Waterhouse 2002). After surgery, rats were housed individually and left 1 or 2 wk to recover prior to any recording session.

DATA ACQUISITION. At least 2 h before the beginning of the recording session, animals were placed in a clear Plexiglas circular cage (Instech Labs) that was different from the home cage. Neuronal activity was recorded from the eight micro-electrodes simultaneously using the multi-channel data-acquisition system from Plexon (Dallas, TX). Data-acquisition parameters (amplification, filtering, and threshold of detection) were set independently for each micro-electrode. Electrical stimulation (duration: 0.1 ms) was delivered to the whisker-pad every 2 s via the whisker-pad electrode. The intensity of stimulation (0.51 ± 0.06 mA) was adjusted for each animal until neuronal responsiveness to whisker-pad stimulation was confirmed. During the recording session, the whisker pad was stimulated every 2 s, and all the waveforms crossing the detection threshold were stored for offline spike-sorting using Plexon software. To quantify the behavioral effect of MPH, we also videotaped each animal throughout each recording session. Each video was time-stamped with a video timer.
analyses experiments, pontamine sky blue (PSB, 2%) dye was infused through probes to mark their location. Animals were perfused with formaldehyde and brains were extracted. Parasagittal slices (30 μm) were cut with a microtome, stained with neutral red, dehydrated, and mounted in Permount (SP15-500, Fisher) for anatomical localization of the electrode array or microdialysis probe (Fig. 1).

**Locomotor activity**

The behavior of each animal was recorded during each recording session and time-stamped with a video timer synchronized to all recorded data channels. Horizontal locomotion was quantified as the number of half-turns executed during each time interval (15 min). Vertical locomotion was also quantified as the number of rearings. However, rearings were infrequent, and we decided not to present these data in the present report. This assessment of locomotor activity is routinely used when animals are housed in circular cages (Darracq et al. 2001).

**Statistics**

For the locomotor activity and microdialysis, graphs represent means ± SE of the data obtained for all animals (n = 5 for the microdialysis and n = 7 for the locomotor activity). Variations across time were analyzed using one-way repeated-measure ANOVA followed by a Dunnett’s multiple comparison test in which data obtained for each time interval was compared with the mean of data obtained before MPH administration.

For the electrophysiology, quantified data (Figs. 4C, 5C, and 6) represent the means ± SE of data obtained from each unit (n = 56 for 1 mg/kg MPH and n = 67 for 5 mg/kg MPH). For each unit, data were obtained from a single PSTH built from the time interval specified in the figure. As several components of the basal and sensory-evoked discharge did not follow a normal distribution (according to Kolmogorov-Smirnov test), Wilcoxon signed-rank test was used to compare postsaline and post-MPH responses to control responses. In cases where postsaline responses differed significantly from control responses, we also compared post-MPH responses to postsaline responses using the same test.

For the correlation analyses between locomotor activity and neuronal discharge, the locomotor activity of each rat was quantified for each 15-min time interval, and neuronal data were obtained for each unit from PSTHs built for the same time interval (as the videotape of the behavior was synchronized to the recording). The mean of neuronal responses obtained for each rat was then compared with its locomotor response using a nonparametric correlation analysis (Spearman). Correlations under control conditions were analyzed using the six 15-min time intervals before and after the saline
RESULTS

MPH increase in NE extracellular levels in the SI cortex

The intraperitoneal injection of saline did not significantly alter NE levels in the SI cortex. By contrast, NE levels were significantly increased after the administration of each dose of MPH tested (Fig. 2). For the 1 mg/kg dose, the MPH-induced increase in NE levels was maximal during the first 20 min postinjection (+65 ± 17%) and remained significantly elevated 0–40 min after the drug injection (P < 0.01). NE levels returned to baseline 80 min postinjection. For the 5 mg/kg dose, the MPH-induced increase in NE levels was maximal 20–40 min after the injection (+100 ± 33%) and remained significant 20–100 min after the drug injection (P < 0.05) with a return to preinjection levels by 3 h after drug administration.

SI cortex neuronal responses to whisker-pad stimulation under control conditions and after a saline injection

We conducted 14 recording sessions (1 experiment for each dose of MPH in 7 rats) and obtained 210 recordings, 123 of which were identified as originating from single neurons and, as such, included in our study. During the control period, the average basal firing rate of the single units was 1.6 ± 0.14 Hz. In 98% of the units (n = 120/123), the stimulation of the whisker pad elicited a short-latency excitation, which started 4.7 ± 0.23 ms after the stimulation and lasted 27 ± 1.3 ms. The average magnitude of the response was 3.8 ± 0.31 Hz above basal firing. In 84% of the units (n = 103/123), the whisker-pad stimulation also elicited a postexcitatory inhibition, which started 36 ± 1.5 ms after the stimulus presentation and lasted 63 ± 2 ms. During this period of inhibition, the average suppression of neuronal discharge was 0.49 ± 0.05 Hz below basal firing. Finally, in 89% of the units (n = 109/123), the response to whisker-pad stimulation also included a long-latency excitation. The long-latency excitation started 105 ± 2.6 ms after the stimulus presentation and the magnitude of this response was 0.58 ± 0.06 Hz above basal firing. Such complex, tri-phasic responses to tactile stimulation are observed routinely in somatosensory cortical neurons of waking animals (Chapin et al. 1981).

The intraperitoneal administration of saline increased the locomotor activity of the animals during the first 15 min postinjection (Fig. 3) and induced a small, albeit significant, decrease in the magnitude of the short-latency excitation (−10.3 ± 2.2%, P < 0.0001). By contrast, saline had no significant effect on other aspects of the spontaneous or sensory-evoked discharge. Moreover, we compared the mean of neuronal responses obtained from each rat to its behavioral response measured every 15-min before and after the saline injection (Table 1) and found a negative correlation between the magnitude of the short-latency excitation and the amplitude of locomotor activity, suggesting that the suppression of the short-latency excitation observed after the saline injection resulted from the behavioral activation of the animal.

TABLE 1. Nonparametric correlation analysis (Spearman) between neuronal activity in SI cortex and locomotor activity measured before and after the saline injection

<table>
<thead>
<tr>
<th>Basal Firing</th>
<th>Magnitude</th>
<th>Latency</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>Short-latency excitation</td>
<td>r = −0.2923</td>
<td>r = 0.05082</td>
<td>r = 0.1195</td>
</tr>
<tr>
<td>P = 0.007</td>
<td>P = 0.6462</td>
<td>P = 0.2788</td>
<td></td>
</tr>
<tr>
<td>Post-excitatory inhibition</td>
<td>r = −0.03</td>
<td>r = 0.0497</td>
<td>r = −0.004903</td>
</tr>
<tr>
<td>P = 0.7865</td>
<td>P = 0.6575</td>
<td>P = 0.9651</td>
<td></td>
</tr>
<tr>
<td>Long-latency excitation</td>
<td>r = −0.02951</td>
<td>r = −0.01501</td>
<td></td>
</tr>
<tr>
<td>P = 0.7899</td>
<td>P = 0.8922</td>
<td></td>
<td></td>
</tr>
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P = 0.18641 and r = 0.145 for basal firing.
while, no significant correlation was found for other aspects of
the spontaneous or sensory-evoked discharge.

**Suppression of mid- and long-latency sensory-evoked
responses of SI cortical neurons by MPH (1 mg/kg)**

The effect of MPH (1 mg/kg) on the behavior of the rats was
similar to that of saline (Fig. 3). At that dose, MPH did not
significantly alter the magnitude of the short-latency excitation (in
comparison to the saline injection), but it reduced the magnitude
of both the postexcitatory inhibition (−13.6 ± 5.9%, \(P = 0.015\))
and the long-latency excitation (−35.3 ± 8.3%, \(P < 0.0001\))
evoked by whisker-pad stimulation (see Figs. 4 and 6). MPH at 1
mg/kg also significantly decreased the duration of the postexcita-
tory inhibition (−4.9 ± 3.4 ms, \(P = 0.0348\)).

**Alterations of sensory-evoked responses of SI cortical
neurons by MPH (5 mg/kg)**

At the higher dose of 5 mg/kg, MPH significantly increased
locomotion during the first 45 min postinjection. Locomotor

**FIG. 4.** Time course of the effect of MPH (1 mg/kg) on basal and sensory-evoked discharge of SI cortical single units. Electrical stimulation of the whisker-pad was
delivered every 2 s and neuronal activity was recorded during a 45-min control period, a 45-min postsaline injection period, and a 90-min post-MPH injection period.
A: this peri-stimulus raster shows the firing of a single neuron in response to the whisker-pad stimulation for the duration of the recording session. Arrows, time of the
saline and MPH administrations. This particular single unit displayed a short-latency excitation, a postexcitatory inhibition and a long-latency excitation in response to
the whisker-pad stimulation. This response was not altered by saline injection, but MPH administration reduced the duration of the postexcitatory inhibition and decreased
the magnitude of the long-latency excitation. Additional effects of saline or MPH administration were observed on other units, as illustrated in B and C. B: each peristimulus
time histogram (PSTH) represents the response of the entire population of recorded units (n = 56) for consecutive 15-min time intervals during the control (gray), postsaline (light gray) and post-MPH (dark gray) periods. Arrows, time of the saline and MPH administrations. The basal firing rate (mean firing rate during the
200 ms preceding whisker-pad stimulation) was subtracted from the firing rate so that each component of the response (short-latency excitation, postexcitatory inhibition and long-latency excitation) appears clearly on the histograms. C: basal firing rate of SI cortical single-units, as well as the magnitude, latency, and duration of each
component of the response evoked by whisker-pad stimulation (short-latency excitation, postexcitatory inhibition and long-latency excitation) were quantified every 15-min during the control, postsaline and post-MPH periods. Data were normalized by the average response measured during the control period and are expressed as
percentages. Arrows, time of saline (dashed) and MPH (solid) injections.
activity was maximal from 15 to 30 min after the injection and returned to control levels 90 min post-MPH administration (Fig. 3). At that dose, MPH had effects on stimulus-evoked discharge similar to those induced by the 1 mg/kg dose (see Figs. 5 and 6). It suppressed both the postexcitatory inhibition (−34.9 ± 11.2%, P = 0.0028) and the long-latency excitation (−23.7 ± 14.5%, P = 0.0122), and it also decreased the duration of the postexcitatory inhibition (−7.1 ± 3.6 s, P = 0.0176).

In addition to those effects, MPH at 5 mg/kg significantly increased the basal firing rate of SI cortical units (±30.4 ± 7.9%, P = 0.0024) and suppressed the short-latency excitation (−23.1 ± 7.1 vs. −8.4 ± 3.0% for saline; P = 0.046). Interestingly, MPH clearly increased the latency of the short-latency excitation in 24% of the recorded units (n = 16/67). The presence of this effect on this distinct population of neurons resulted in the appearance of a second peak in the short-latency excitation on population histograms (Fig. 5B), although this effect was not statistically significant when all units were analyzed together (1.2 ± 0.53 ms, P = 0.125). Finally, the latency of the long-latency excitation was significantly decreased (−20.7 ± 5.5 ms, P = 0.0001).

We also compared the mean of neuronal responses obtained from each rat to its behavioral response measured every 15 min after the MPH (5 mg/kg) injection and found significant correlations between the amplitude of the behavioral response and the basal firing rate as well as the magnitude and onset latency of the different components of the whisker-evoked response (Table 2). However, this analysis does not necessarily indicate that variations in neuronal responses result exclusively from variations in behavior. Indeed, these correlations may simply result from the fact that variations in neuronal and behavioral responses both resulted from the MPH administration. Interestingly, the behavioral response and the magnitude of the short-latency excitation were positively correlated after MPH, whereas they were negatively correlated before the drug was administered (Table 1). An analysis of covariance revealed that the relationship between the behavior and the magnitude of the short-latency excitation observed before MPH administration was significantly different from the relationship observed after the drug administration [F(1,80) = 6.34, P = 0.01379]. Therefore MPH may enhance the short-latency excitation, whereas locomotor activity suppresses this response. Such a direct action of MPH on the short-latency excitation would be partially masked by the impact of MPH-induced behavioral activation on this response.

**Discussion**

To our knowledge, this study is the first to analyze neurophysiological and neurochemical actions of MPH in a primary sensory cortical area (i.e., the SI cortex) of freely behaving animals. Our general working hypothesis is that MPH, via increased NE efflux, affects sensory signal transmission and that such an outcome is important in considering the basis of MPH’s therapeutic action in ADHD treatment. We tested low and moderate doses of MPH (1 and 5 mg/kg, respectively), both of which produced significant increases in extracellular levels of NE in the SI cortex. Moreover, MPH selectively suppressed the mid- and long-latency components of sensory-driven responses in SI cortical neurons. These effects were observed with both doses of MPH and did not seem to depend on drug-induced modifications of the animal exploratory behavior.

**Impact of locomotor activity and MPH administration on the short-latency excitation**

In agreement with previous studies (Drouin and Waterhouse 2004; Fanselow and Nicoletis 1999), the amplitude of the short-latency excitation was influenced by the behavioral state of the animal. Under control conditions, we observed that the magnitude of the short-latency excitation was negatively correlated with the locomotor activity of the animal. As a result, the intraperitoneal injection of saline, which increased locomotion, also produced a significant suppression of the short-latency excitation. At 1 mg/kg, MPH increased the locomotion and suppressed the short-latency excitation to the same extent as a saline injection. At 5 mg/kg, the MPH-induced locomotor response was significantly larger than the saline-induced response. Similarly, MPH-induced suppression of the short-latency excitation was significantly larger than the saline-induced suppression. However, covariance analysis revealed that MPH (5 mg/kg)-induced suppression of the short-latency excitation was not as large as predicted, considering the amplitude of the behavioral response produced by the drug. This suggests that a direct enhancing effect of MPH may counterbalance the suppression induced by the behavior. In agreement with this hypothesis, we have found that MPH (5 mg/kg) can enhance the sensory-evoked short-latency excitation of SI cortical neurons in anesthetized animals (Waterhouse et al. 2004). Moreover, several in vivo studies have reported NE-mediated enhancement of short-latency, synaptically driven excitatory responses of cells in the SI cortex of anesthetized or quietly resting animals (Devilbiss and Waterhouse 2000, 2004; Lecas 2004; McCormick et al. 1991; Waterhouse and Woodward 1980; Waterhouse et al. 2000).

**Impact of MPH administration on the postexcitatory inhibition**

The administration of MPH significantly suppressed the postexcitatory inhibition in a dose-dependent manner. This effect likely resulted from the enhancement of noradrenergic transmission in the SI cortex. Indeed, several studies have demonstrated the involvement of intracortical GABAergic interneurons in the postexcitatory inhibition (Porter et al. 2001; Swadlow 2003), and NE application has been found to decrease the amplitude of evoked inhibitory postsynaptic potentials in the SI cortex via adrenergic receptors located on GABAergic presynaptic terminals (Bennett et al. 1998). However, previous studies showed that exploratory behavior could suppress the postexcitatory inhibition (Drouin and Waterhouse 2004; Fanselow and Nicoletis 1999). In our study, the amplitude of the postexcitatory inhibition was not significantly correlated with the locomotor activity under control conditions, suggesting that the behavioral state of the animal was not the main factor contributing to the variability of this neuronal response. Moreover, MPH (1 mg/kg) did not increase locomotor activity (compared with the saline injection) but significantly suppressed the postexcitatory inhibition (decreased magnitude and duration). However, the impact of MPH (1
FIG. 5. Time course of the effect of MPH (5 mg/kg) on basal and sensory-evoked discharge of SI cortical single units. Electrical stimulation of the whisker-pad was delivered every 2 s and neuronal activity was recorded during a 45-min control period, a 45-min postsaline injection period, and a 180-min post-MPH injection period. A: this peri-stimulus raster shows the firing of a single neuron in response to the whisker-pad stimulation for the duration of the recording session. Arrows, time of the saline and MPH administrations. This particular single unit displayed a short-latency excitation, a postexcitatory inhibition, and a long-latency excitation in response to the whisker-pad stimulation. This response was not altered by saline injection but MPH administration shortened the postexcitatory inhibition and reduced the magnitude of the long-latency excitation. Additional effects of saline or MPH administration could be observed on other units, as illustrated in B and C. B: each PSTH represents the response of the entire population of recorded units (n = 67) for consecutive 15-min time intervals during the control (gray), the postsaline (light gray), and the post-MPH (dark gray) period. Arrows, time of the saline and MPH administrations. The basal firing rate (mean firing rate during the 200 ms preceding whisker-pad stimulation) was subtracted from the firing rate so that each component of the response (short-latency excitation, postexcitatory inhibition and long-latency excitation) appears clearly on the histograms. C: basal firing rate of SI cortical single units, as well as the magnitude, latency, and duration of each component of the response evoked by whisker-pad stimulation (short-latency excitation, postexcitatory inhibition, and long-latency excitation) were quantified every 15-min during the control, postsaline and post-MPH periods. Data were normalized by the average response measured during the control period and are expressed as percentages. Arrows, time of saline (dashed) and MPH (solid) injections.
mg/kg) on the postexcitatory inhibition was limited, and the time courses of the effects of MPH (5 mg/kg) on this inhibition and on the behavior were very similar. As a result, we cannot completely exclude the possibility that part of the effect of MPH on the postexcitatory inhibition resulted from drug-induced changes in behavior.

Impact of MPH administration on the long-latency excitation

The administration of MPH significantly suppressed the long-latency excitation. It is likely that this effect also resulted from the enhancement of the noradrenergic transmission. Indeed, event-related potential studies in rats have shown that dorsal noradrenergic bundle lesions specifically increase negative potentials in the cortex occurring 50–100 ms after sensory stimulus presentation (Ehlers and Chaplin 1992), thus suggesting that NE transmission normally suppresses these responses. Interestingly, this NE-induced suppression of negative potentials was specific to the presentation of frequent stimuli and did not occur when novel or infrequent stimuli were presented. The impact of MPH on the long-latency excitation may be secondary to the suppression of the postexcitatory inhibition. Indeed, in vitro recording studies suggest that the long-latency excitatory response results directly from a postinhibitory rebound excitation (Castro-Alamancos and Connors 1996; Morin and Steriade 1981; Spain et al. 1991). Alternatively, a similar phenomenon occurs in VPM thalamocortical relay neurons in response to GABAergic inhibition from the reticular thalamic nucleus (Warren and Jones 1994), which may also participate in the induction of the long-latency

![FIG. 6. Quantification of the effect of saline and MPH (1 and 5 mg/kg) on basal and sensory-evoked discharge of SI cortical single units. The basal firing rate of SI cortical single units, as well as the magnitude, latency, and duration of each component of the response evoked by the whisker-pad stimulation (short-latency excitation, postexcitatory inhibition, and long-latency excitation) were quantified (see METHODS) during a 45-min period after the saline injection or the administration of each dose of MPH (1 or 5 mg/kg). Bar graphs represent the mean variation (±SE) from control values measured during the postsaline (white bars) and each post-MPH (light gray for 1 mg/kg and dark gray for 5 mg/kg) 45-min periods. Variations in basal firing and response magnitude are expressed as a percentage of the mean of control values. Variations in latency and duration are expressed in milliseconds. Wilcoxon signed-rank test was used to determine if variations from control were significantly different from 0 (*, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$). For the magnitude of the short-latency excitation, the saline injection induced significant variation from the control value. Therefore we also analyzed if the MPH administration induced significant variations from saline values with the Wilcoxon signed-rank test (°, $P < 0.05$).

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**TABLE 2.** Non-parametric correlation analysis (Spearman) between neuronal activity in SI cortex and locomotor activity measured after the administration of MPH (5 mg/kg)

<table>
<thead>
<tr>
<th>Basal Firing</th>
<th>Magnitude</th>
<th>Latency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-latency excitation</td>
<td>$r = 0.3161$</td>
<td>$r = 0.6952$</td>
<td>$r = -0.01889$</td>
</tr>
<tr>
<td>$P = 0.0414$</td>
<td>$P &lt; 0.0001$</td>
<td>$P = 0.9055$</td>
<td></td>
</tr>
<tr>
<td>Post-excitatory inhibition</td>
<td>$r = 0.6297$</td>
<td>$r = 0.305$</td>
<td>$r = -0.2269$</td>
</tr>
<tr>
<td>$P &lt; 0.0001$</td>
<td>$P = 0.0495$</td>
<td>$P = 0.1484$</td>
<td></td>
</tr>
<tr>
<td>Long-latency excitation</td>
<td>$r = -0.7543$</td>
<td>$r = -0.3451$</td>
<td>$r = 0.2097$</td>
</tr>
<tr>
<td>$P &lt; 0.0001$</td>
<td>$P = 0.0292$</td>
<td>$P = 0.015$</td>
<td></td>
</tr>
</tbody>
</table>

$P = 0.015$ and $r = 0.373$ for basal firing.
excitation in the SI cortex (Grenier et al. 1998; Steriade et al. 1998). Interestingly, the conductance involved in the postinhibitory rebound excitation (i.e., the \( I_h \) current) (Spain et al. 1991) is regulated by beta-adrenergic receptors in the VPM thalamus (McCormick and Pape 1990). Therefore MPH-induced suppression of the long-latency excitation in the cortex may also involve MPH-induced increase in NE levels in the VPM thalamus.

As for other influences on the sensory-evoked discharge of SI cortical neurons, previous studies showed that exploratory behavior could suppress the long-latency excitation (Drouin and Waterhouse 2004; Fanselow and Nicolelis 1999). However, in the present study, the amplitude of the long-latency excitation was not significantly correlated with the behavior under control conditions, suggesting that the behavioral state of the animal was not a main factor contributing to the variability of this neuronal response. Moreover, MPH significantly suppressed the long-latency excitation without increasing locomotor activity (after the 1 mg/kg dose and 90–180 min after the 5 mg/kg dose). Therefore MPH likely suppressed the long-latency excitation independently from its action on locomotion.

**Differences between the effects of MPH and those previously observed with cocaine**

Similarities between the pharmacological properties of MPH and cocaine have been emphasized in light of concerns regarding the increased number of MPH prescriptions to children. Indeed, cocaine and MPH are both catecholamine reuptake inhibitors and have similar affinities for DA and NE transporters (Lille et al. 2003). The main difference between cocaine and MPH is that cocaine is also a potent reuptake inhibitor of serotonin, whereas MPH is not. Cocaine influences on SI cortical neuronal responses were analyzed in a previous study and found to be qualitatively different from those of MPH (Bekavac and Waterhouse 1995; Drouin and Waterhouse 2004; Waterhouse et al. 1996). Indeed, in those experiments, cocaine dramatically enhanced long-latency excitation, whereas the present study showed that MPH suppressed this response. The cocaine-induced enhancement of the long-latency excitation likely resulted from the action of the drug on serotonergic transmission as it was no longer observed after lesion of serotonergic fibers by PCPA (Waterhouse et al. 1996).

**How do 1 and 5 mg/kg MPH compare with clinical doses used in ADHD patients?**

Consistent with its classification as a psychostimulant, MPH has been reported to stimulate exploratory behavior when given at high doses (Davids et al. 2002; Gerasimov et al. 2000). For many years, the calming effect of psychostimulants in ADHD patients was considered paradoxical. However, it was recently emphasized that therapeutic doses of MPH do not induce hyperactivity in healthy subjects, whereas higher doses can further increase hyperactivity in ADHD patients. Therefore one might consider that for normal experimental animals, a dose of MPH in the therapeutic range for ADHD treatment should be low enough so that increases in exploratory behavior are minimal. In our study, we analyzed the impact of MPH administration on neurochemistry, neurophysiology, and behavior at 1 and 5 mg/kg, considered as low and moderate doses, respectively. Quantification of locomotor activity confirmed that MPH did not significantly alter exploratory behavior at 1 mg/kg. However, at 5 mg/kg, MPH significantly enhanced locomotion with a time course that was consistent with previous reports (Gerasimov et al. 2000). Thus using increased locomotion as an indicator, only the 1 mg/kg dose of MPH may be considered to be within a therapeutically equivalent range for laboratory rats. Moreover, ongoing behavioral studies in rats have shown that MPH at doses of 1–2 mg/kg improve performance in a sustained attention task (Shumsky et al. 2004), whereas higher doses (5 mg/kg) lead to a decrease in task performance associated with locomotor hyperactivity. Finally, clinical studies indicate therapeutic efficacy of MPH when plasma levels are within the range of 8–40 ng/ml (Swanson and Volkow 2001). Preliminary data show that these plasma levels can be achieved in rats after the intraperitoneal administration of MPH at 1 mg/kg and lower (Berridge et al. 2006). Although the 1 and 5 mg/kg doses of MPH seem to be different with regard to their therapeutic efficiency, they exerted similar effects on the basal and sensory-evoked discharge of somatosensory cortical neurons. This suggests that the high dose of MPH has the same influence on sensory processing as the low dose, but it also triggers behavioral side effects that limit its usefulness in the treatment of ADHD.

**How might the observed effects of MPH prove beneficial in ADHD?**

Along with hyperactivity/impulsivity and attention deficits, ADHD is associated with impairments in working memory, decision making, and response inhibition, most of which can be improved by MPH treatment (Mehta et al. 2001; Solanto 1998). Behavioral studies in rodents and primates have shown that these cognitive processes involve NE and DA in different regions of the prefrontal cortex. In agreement with these studies, most imaging and electroencephalography studies have associated cognitive impairments in ADHD patients with dysfunctions of fronto-striatal circuitry and the generation of the P300 (also known as P3), a positive waveform in the electroencephalogram occurring ~300 ms after the stimulus presentation in relation to the cognitive demand of the task (Barr et al. 2003). In addition to these alterations, ADHD patients also display increased cerebral blood flow in somatosensory areas of the cortex; an outcome that can be normalized after extended MPH treatment and may be related to the inability of ADHD patients to suppress responsiveness to irrelevant sensory stimuli (Lee et al. 2005). In agreement with this hypothesis, psychophysiological studies showed that children with ADHD exhibit larger somatosensory evoked potentials than control subjects. They also tend to be tactile defensive and are less skilled in tactile tasks (Parush et al. 1997). More detailed studies were performed with auditory stimuli showing that in addition to alterations in late components of auditory event-related potentials (ERPs) (such as the P300), ADHD patients show anomalies in the regulation by attention of the N1 component (also referred to as N100, N120, or N140), a negative waveform in the electroencephalogram occurring ~100 ms after the stimulus presentation that originates partly in primary auditory cortical areas (Kemner et al. 2004). In healthy control subjects, the amplitude of the N1 component is generally higher in response to infrequent or attended stimuli.
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than in response to frequent and nonattended stimuli. Such a regulation is altered in patients with ADHD (Barry et al. 2003; Kemner et al. 2004; Smith et al. 2004). Although no direct correlation can be made between the N1 component of sensory ERPs in humans and the sensory-evoked long-latency excitation recorded in our study, it is interesting that both types of responses occur within the same latency after stimulus presentation (~100 ms). Therefore MPH may help restore the regulation of this N1 component in ADHD patients, who have difficulty discriminating between salient and irrelevant environmental stimuli.

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