Staying in Touch With Methylphenidate: ADHD and Sensory Processing. Focus on “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 et al. (this issue of J. Neurophysiol. p. 622–632) provide the first analysis of the neurochemical and neurophysiological effects of the stimulant medication, methylphenidate (MPH), in sensory cortex of freely behaving animals. MPH has been prescribed to children and adults with Attention Deficit Hyperactivity Disorder for decades (under the brand name Ritalin), yet little is known about how this compound alters sensory processing. Drouin et al. utilized a well-characterized system—the barrel field somatosensory cortex (S1) in rats—to examine how MPH alters cortical response to whisker stimulation. They administered saline, or a relatively low (1 mg/kg ip) or moderate (5 mg/kg ip) dose of MPH while measuring extracellular norepinephrine (NE) levels in S1, recording neuronal activity in S1, and assessing locomotor behavior in freely moving rats. The authors found that the lower dose of MPH increased NE release in S1 and suppressed long-latency neuronal responses without altering locomotor behavior. The higher dose similarly increased NE and suppressed the long-latency responses but also induced locomotor activation and had complex interactions on the initial excitatory responses of S1 neurons. As therapeutic doses of MPH do not increase locomotor activity in children, it is likely that the lower dose is the more relevant to current ADHD therapy. Suppression of longer-latency responses may be of particular relevance to interactions of S1 with other brain regions. The authors suggest that MPH may improve sensory attention by increasing NE release in S1 cortex and suppressing “noise.” This interpretation is consistent with the clinical literature, as ADHD patients are often tactile defensive and exhibit disinhibited somatosensory evoked potentials (Parush et al. 1997) and increased regional cerebral blood flow in S1 that is normalized by stimulant medication (Lee et al. 2005).

Stimulant medications such as MPH are currently being prescribed to ~2.5 million children in the United States, yet there has been surprisingly little research on the mechanism of action of these compounds. For years it was assumed that MPH had a paradoxical effect in ADHD children—a stimulant having calming actions. However, it is now well established that this is not a paradoxical effect in ADHD but rather an effect of dose, and that low, oral doses of MPH focus behavior and attention in normal individuals as well as those with ADHD (Rapport and Inoff-Germain 2002). Another myth was that stimulants showed species differences, focusing behavior in humans but increasing locomotor activation in rodents. It is now known that the doses of MPH given in most previous rodent studies were too high and that low doses (especially when given orally) actually reduce or have no effect on locomotor activity (Kuczenski and Segal 2002) and improve prefrontal cortical cognitive abilities in rats as well as in humans (Arnsten and Dudley 2005; C. Berridge, personal communication). The current study found that a low dose of MPH—one that had no effect on locomotor activity—suppressed the long-latency responses of S1 neurons. This study in behaving animals provides a link between the clinical use of MPH and previous in vitro studies of NE actions in S1 slice preparations that similarly found suppressive effects with β adrenergic receptor stimulation e.g., (Devilbiss and Waterhouse 2000). The results are also consistent with a classic finding by Foote and colleagues showing that NE increases the signal to noise ratio of responding in auditory cortex, mostly by suppressing noise (Foote et al. 1975).

The authors note that MPH is administered systemically in this study, thus blocking catecholamine reuptake and facilitating catecholamine transmission throughout the neuroaxis. Thus drug effects on S1 neurons may also arise from MPH actions in other brain regions connected with the S1 cortex. Drouin et al. raise the possibility that some of these actions may occur in VPM thalamus, which receives a dense NE innervation and projects directly to S1. They posit that the suppression of the long-latency excitation may involve β adrenergic receptor-mediated effects on cAMP/kin mechanisms in thalamus (McCormick and Pape 1990). MPH also may indirectly affect S1 through actions in prefrontal cortex (PFC), facilitating PFC gating of S1 responses. Low doses of MPH increase extracellular levels of both NE and dopamine in PFC and improve PFC cognitive function (Arnsten and Dudley 2005). The PFC projects back to sensory cortices where it has a “top-down” gating influence on sensory processing. Thus patients with PFC lesions, like ADHD patients, have disinhibited somatosensory evoked potentials (Yamaguchi and Knight 1990). Low doses of MPH may strengthen PFC regulatory output and thereby inhibit responses to irrelevant sensory stimulation.

It would be interesting to determine how S1 neurons would respond in the presence of MPH if the animals were required to attend to the whisker stimulation, e.g., perform a somatosensory discrimination. It is possible that under these conditions low doses of MPH might facilitate the initial excitatory response of S1 neurons and perhaps decrease the suppression at longer latencies as well.

In summary, new research with low doses of MPH in animals has begun to reveal the mechanisms by which stimu-
lant medications may alter attentional processing in humans. MPH may have both direct effects in S1 as well as indirect effects through bottom up (VPM thalamus) and top-down (PFC) influences on S1 responsivity. The excellent correspondence between findings in animals and patients encourages the relevance of the basic research to human drug actions.

REFERENCES

Arnsten AFT and Dudley AG. Methylphenidate improves prefrontal cortical cognitive function through a2 adrenoceptor and dopamine D1 receptor actions: relevance to therapeutic effects in Attention Deficit Hyperactivity Disorder. Behav Brain Funct 1: 2, 2005.


