Serotonin and the Therapeutic Effects of Ritalin

Gainetdinov et al. (1) reported that in dopamine transporter (DAT) knockout (KO) mice, which have elevated dopamine (DA) tone and are hyperactive, both psychostimulants and drugs that increase serotonin concentration in the brain decreased locomotor activity. They therefore suggested that the calming effects of psychostimulants in the DAT-KO mice are due to their ability to increase serotonin concentration, that the DAT-KO mouse may be a useful model for individuals with attention-deficit hyperactivity disorder (ADHD), and that the so-called paradoxical calming effect of psychostimulants such as methylphenidate (Ritalin) in ADHD is due to their serotoninergic effects.

A central problem with this proposal is that unlike cocaine and amphetamine, methylphenidate does not increase the extracellular serotonin concentration in the brain (2). The affinity of methylphenidate for the serotonin transporter is very low (3), and if augmentation of serotonin did play an important role in the therapeutic effects of psychostimulants, one would expect serotonin transporter inhibitors to be beneficial in the treatment of ADHD, which they are not (4). Another problem with the interpretation is the very notion that the clinical effects of methylphenidate are paradoxical: children with ADHD respond to methylphenidate as non-responsive children do, as was shown some two decades ago (5).

We question, too, whether the experimental results of Gainetdinov et al. are directly relevant to the therapeutic effects of methylphenidate. The methylphenidate doses given to the DAT-KO mice were more than three orders of magnitude higher than the doses given in the treatment of ADHD (30 mg/kg intraperitoneally in the mice versus 0.1 to 1 mg/kg orally in human patients). The temporal course of methylphenidate’s calming effects in the DAT-KO mice was very different from those of cocaine, amphetamine, or the serotonergic drugs. Whereas the latter drugs exerted an almost immediate calming effect, methylphenidate took more than 30 min to reduce locomotor activity in the DAT-KO mice and had its maximal calming effects 3 hours after its administration, a time at which the therapeutic effects of methylphenidate are dissipating in ADHD patients (6). The time of onset for methylphenidate’s locomotor effects in the wild-type animal, by contrast, was similar to those of cocaine and amphetamine.

Hence, a pharmacokinetic explanation for the differences in the DAT-KO mice is unlikely; rather, those differences suggest that the calming effects of methylphenidate stem from a distinct mechanism relative to those of drugs that are known to increase serotonin concentration.

In sum, linking the calming effects of serotonergic drugs in DAT-KO mice with the therapeutic effects of methylphenidate in ADHD patients may be unwarranted. There is no evidence that methylphenidate increases brain serotonin, nor is there evidence that pure serotonergic drugs are beneficial in ADHD. On the other hand, the work of Gainetdinov et al. in the DAT-KO mice clearly does confirm the important role of serotonin in modulating DA’s regulation of locomotor activity (7).

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Response: Volkow et al. raise a number of arguments against our conclusions regarding the effect of serotonin (5-HT) in the DAT-KO mice (1). All of those arguments are subject to question, however. Although methylphenidate is commonly believed to affect primarily the DA system through blockade of the DAT, evidence from neurochemical, histochemical, electrophysiological, and behavioral studies suggests that this psychostimulant can affect the noradrenergic and serotonergic systems as well (2–5). Thus, the behavioral effects of methylphenidate are unlikely to be explained by only one neurotransmitter or adaptation process (6). In vitro ligand binding data with the rat DAT do indeed indicate that methylphenidate’s affinity for the DAT is higher than its affinity for the serotonin transporter, but the measured magnitudes of those differences have varied considerably, even within the same lab (7, 8). By comparison, our studies were conducted in mice, and the potential confounding differences between the drug’s in vitro and in vivo potencies need to be borne in mind.

The study (5) cited by Volkow et al. that demonstrated that methylphenidate at doses of 10 to 30 mg/kg failed to increase extracellular 5-HT in rat striatum also deserves closer examination. Extracellular levels of this monoamine are notoriously difficult to measure in brain tissue (9), and the potentially small effect of methylphenidate could easily have been missed in (5). The precise anatomical location responsible for the ability of the increased 5-HT to exert a calming influence in the DAT-KO mice is also not known and may not be localized to the striatum. In the DAT-KO mice (1), methylphenidate did not affect extracellular DA levels, but it nonetheless exerted potent attenuation in locomotion—an effect that we showed could be mimicked by raising serotonergic tone in the brains of these animals by administration of 5-HT precursors or selective 5-HT reuptake blockers, or even by direct activation of 5-HT receptors. Although we did not establish the ultimate molecular mechanism, we demonstrated that depletion of 5-HT attenuated the calming effects of methylphenidate. Therefore, a role for 5-HT in the pharmacological effects of psychostimulants in DAT-KO mice is reasonable.

Volkow et al. question whether the response of patients with ADHD to psychostimulants is really “paradoxical.” The study most commonly cited to support such skepticism, by Rapoport et al. (10), used 14 normal prepubescent boys as subjects. In those subjects, a single dose (0.5 mg/kg) of dextroamphetamine reduced locomotor activity and improved performance on several cognitive tests, findings that were interpreted to imply that normal individuals and ADHD patients respond in the same manner to psychostimulants. That interpretation may be oversimplified, however, because no systematic study has compared the dose-response relationships between these two subject populations. What is known is that when normal adults are administered the same doses of methylphenidate (0.3 to 1 mg/kg) or dextroamphetamine (0.1 to 0.6 mg/kg) that are prescribed to pediatric ADHD patients, the doses are stimulatory (11–13). Wang et al. (14) reported that when methylphenidate was given intravenously to cocaine abusers, it induced a “high” similar to that of cocaine, and Volkow et al. (11, 12), using positron emission tomography, showed that methylphenidate is effective in blocking the DAT in human brains (ED50 = 0.075 mg/kg, intravenous; 0.25 mg/kg, oral) and that these same doses

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produce “highs,” restlessness, and “rushes”—behavioral manifestations that can hardly be considered “calming.” Collectively, these data clearly suggest that the doses of methylphenidate or amphetamine used in ADHD patients are stimulatory in normal adults and that, at the same time, they may have a “calming” effect in certain patients.

Volkow et al. correctly observe that the doses of methylphenidate used in our studies are higher than those administered to ADHD patients; as is well documented (5, 8, 11–13), much higher doses of cocaine and methylphenidate are usually required in rodents to study the behavioral effects of psychostimulants. These differences are probably attributable to species-specific pharmacodynamic and pharmacokinetic properties of these psychostimulants. Their comment also seems to imply that the temporal responses of the wild-type mice to methylphenidate better approximate those of ADHD patients than those of the DAT-KO mice. Swanson et al. (15), however, reported that responses of patients to methylphenidate are noticeable within the first 30 min after drug administration, peak at 2 hours, and have a “behavioral half-life” of 4 hours—almost identical to the pattern observed in the DAT-KO mice. By contrast, the maximum stimulatory effect in the wild-type animals occurred within 5 min after drug administration and this response disappeared within 2 hours.

As to the possible role of serotonergic drugs in treating ADHD, the data in the literature are extremely controversial, and without controlled studies (16) it is premature to make emphatic conclusions. Practically all the drugs used to treat ADHD do have a serotonergic component, however, and there is mounting evidence of potential clinical efficacy for drugs with a predominantly serotonergic component of action, such as venlafaxine and buspirone (16, 17). The use of selective 5-HT reuptake inhibitors as an accompaniment to psychostimulant therapy is also becoming more widespread in the treatment of ADHD (16). We hope that our observations in the DAT-KO mice will lead to a more thorough investigation and discussion of the therapeutic mechanisms of psychostimulants, and that these results will increase our understanding of ADHD.

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References
3. M. A. Geyer et al., Brain Res. 85, 139 (1975).

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