Stimulant Actions in Rodents: Implications for Attention-Deficit/Hyperactivity Disorder Treatment and Potential Substance Abuse

Ronald Kuczenski and David S. Segal

Most evidence supports the continued use of stimulants as the best available pharmacotherapy for the treatment of children with attention-deficit/hyperactivity disorder (ADHD), but little is known about possible enduring behavioral and neuroadaptational consequences of long-term stimulant exposure. Although a variety of preclinical studies, particularly those using methylphenidate (MP), have attempted to address these issues, most of these studies have used procedures that might not adequately simulate clinical treatment conditions, and results have not been entirely consistent. In particular, the rationale for selection of MP doses that simulate clinical exposure has not been well defined. We suggest that the use of more appropriate treatment conditions, including doses that result in plasma drug levels comparable to therapeutic levels, will provide a more accurate model for adequately assessing the therapeutic mechanisms and potential long-term consequences of stimulant psychotherapy in the treatment of ADHD.

Key Words: Attention-deficit/hyperactivity disorder, stimulants, substance abuse, methylphenidate, childhood disorders

Most current evidence supports pharmacotherapy as the most effective treatment for attention-deficit/hyperactivity disorder (ADHD) and the use of amphetamine-like stimulants as the best available pharmacotherapy (Biederman et al 2000; Challman and Lipsky 2000; Garland 1998; Safer and Allen 1989; Wigal et al 1999). Although amphetamine (AMPH) itself is efficacious, by far the majority of written prescriptions are for methylphenidate (MP). An estimated 2.8 million children and adolescents (ages 5–18 years) in the United States in 1995 received MP for ADHD (Safer et al 1996), and stimulant treatment in preschoolers (ages 2–4) increased approximately threefold during the early 1990s (Zito et al 2000). Furthermore, ADHD symptoms continue into adulthood in as many as 60% of these children, and continued stimulant therapy remains the most effective treatment throughout the duration of the disorder (Taylor and Russo 2001). Unfortunately, despite the long history and current widespread use of these agents, little is known about possible enduring behavioral and neuroadaptational consequences of this long-term stimulant treatment (Greenhill 200; National Institutes of Health Consensus Development Conference Statement 2001; Safer and Allen 1989).

Enduring Effects of Repeated Exposure

There is, however, considerable evidence that, under some experimental conditions, repeated exposure to amphetamine-like stimulants can have enduring effects in experimental animals (Robinson and Becker 1986; Segal and Kuczenski 1994; Vanderschuren and Kalivas 2000) as well as in humans (Sax and Strakowski 1998; Strakowski and Sax 1998; Strakowski et al 2001). Of particular interest is the progressive enhancement of some stimulant-induced behaviors with repeated administration, a process frequently referred to as behavioral sensitization, which can persist after prolonged periods of drug abstinence (see Robinson and Becker 1986; Segal and Kuczenski 1994; Segal and Schuckit 1983; White and Kalivas 1998 for reviews). It has been suggested that sensitization after repeated administration of AMPH and cocaine, which has been particularly well-documented, might be implicated in the development of stimulant addiction/abuse (Robinson and Berridge 1993). Furthermore, animal studies with behavioral paradigms, such as drug self-administration and conditioned place preference, indicate that repeated administration of psychomotor stimulants might also enhance the reinforcing properties of these drugs. Thus, one particular concern regarding the effects of long-term stimulant exposure in the treatment of ADHD is the possibility that the drug abuse liability of these drugs might be significantly increased (Laviola et al 1999; Schenk and Davidson 1998).

Unfortunately, although MP is the predominant stimulant pharmacotherapy in ADHD, only a few preclinical studies have examined the effects of repeated exposure to MP, and whereas effects similar to those of AMPH and cocaine have been reported by some, other results have not always been consistent. For example, in earlier studies, some investigators observed an increased locomotor response, or locomotor sensitization, after repeated exposure to MP (Gaytan et al 1997; Sripada et al 1998), whereas others did not (Crawford et al 1998; Izenwasser et al 1999). Likewise, an augmented stereotypy response has been observed by some (Browne and Segal 1977; Crawford et al 1998) but not by others (Izenwasser et al 1999; McNamara et al 1993). On the basis of those animal data, it has not been possible to conclude that repeated MP results in the same pattern of long-term consequences that has been well documented for the other amphetamine-like stimulants. It is important, however, to note that the consequences of repeated stimulant administration (i.e., the characteristics of any altered response profile) and, in fact, whether sensitization even develops, are profoundly affected by a variety of experimental factors (Gaytan et al 1999, 2000; Laviola et al 1999; Robinson and Becker 1986; Segal and Kuczenski 1994). Specifically with regard to the use of stimulants in the treatment of ADHD, because the development of sensitization and related behaviors depends on the nature of the treatment regimen, we have questioned to what extent current and previous drug exposure paradigms that have been used to establish persistent behavioral alterations in animal models might be relevant to long-term MP usage in children in the treatment of ADHD (i.e, to what extent these paradigms mirror the conditions associated with clinical treatment and thus have translational utility).

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Administration Routes and Dosing

For example, the clinical treatment of ADHD in adolescence involves oral administration of the drug. In contrast, most preclinical studies use the subcutaneous or intraperitoneal (IP) routes of administration. This difference in route is critically important with regard to assessing the effective dose used, because the oral route results in lower peak drug concentrations and a slower rate of drug accumulation, two components of the pharmacokinetic profile that can affect both the quantitative and qualitative features of the drug response. Furthermore, in contrast to clinical treatment that occurs during the waking hours, most preclinical studies have been conducted during the light phase, the period of normal inactivity in the rat. Because drug effects are being imposed on behavioral and neurochemical substrates that are known to vary significantly as a function of circadian rhythm, this difference can be potentially important. Of particular relevance, the development of locomotor sensitization to MP has been shown to be time dependent, with the most robust sensitization occurring when the drug was administered during the light/inactive phase of the light/dark cycle, whereas no sensitization was observed during the dark/active phase (Gaytan et al 2000). Developmental age during treatment might also play a critical role in determining the effects of long-term stimulant treatment (Bolaños et al 2003; Carlezon et al 2003). For example, in recent studies of the long-term effects of MP treatment in young animals, Brandon et al (2001) administered MP (2 mg/kg, IP) during postnatal days 35–42 and found evidence of an enhanced rewarding effect of subsequent cocaine self-administration. In contrast, Andersen et al (2002) (Carlezon et al 2003) administered the same dose (2 mg/kg IP) during postnatal days 20–35 and found an attenuated rewarding effect of cocaine in a conditioned place preference test. Because route of drug administration, circadian cycle, and these potential age-dependent factors can affect both the quantitative as well as the qualitative effects of subsequent stimulant administration, consideration for these variables should be incorporated into preclinical treatment models to more precisely assess potential consequences of stimulant pharmacotherapy in children.

Equally important within this context, drug dose clearly plays a pivotal role in both the qualitative nature as well as the quantitative features of the acute stimulant response, and it is therefore not surprising that dose is critical in the development and/or expression of chronic stimulant-induced behavioral and neurochemical alterations (Robinson and Becker 1986; Segal and Kuczenski 1994; Segal and Mandell 1974; Segal and Schuckit 1983; White and Kalivas 1998, for reviews). In fact, it has recently been suggested that the results obtained from most previous stimulant studies might not be relevant to effects produced by the therapeutic use of these drugs (Kuczenski and Segal 2001; Volkow and Insel 2003), because they do not adequately take into account therapeutic dosing.

Unfortunately, a reasonable rationale for the selection of relevant doses has not been well defined. One approach that has been used involves extrapolation on a milligrams per kilogram basis from clinical doses. This approach leads to dose selection much lower than is typically used in preclinical studies. Perhaps importantly, "clinical doses" of MP (approximately .5 mg/kg) seem to be near or below threshold for the induction of locomotor activation, although they still affect regional extracellular neurotransmitters (Kuczenski and Segal 2001). Treatment of ADHD through oral administration of the drug, however, results in a much lower MP bioavailability (.23; Srinivas et al 1992) compared with the IP and subcutaneous routes typically used in preclinical studies, thus confounding simple milligrams per kilogram comparisons (see Figure 1). In addition, bioavailability after oral MP in rats seems to be dose dependent, with values as low as .06 at lower "therapeutic" doses (Aoyama et al 1990; Wargin et al 1983). Thus, because of the marked species differences in stimulant pharmacokinetics (Benet et al 1990; Mordenti 1986; Patrick et al 1984; Wargin et al 1983), simple extrapolation on a milligrams per kilogram basis from clinical doses provides, at best, only a crude approximation of the appropriate dose range for preclinical studies. Alternatively, to partially address species differences in pharmacokinetics, particularly the shorter half-life of MP in rats compared with humans (Aoyama et al 1990, 1996; Shaywitz et al 1982; Srinivas et al 1992; Thai et al 1999; Wargin et al 1983), IP doses as high as 5 mg/kg—sufficiently high to increase locomotor activity—have been considered to maintain drug levels within the therapeutic range over a more appropriate interval.

Clearly, drug doses spanning such a relatively broad range (.5–5 mg/kg) can be associated with qualitatively distinct response profiles (summarized in Table 1), emphasizing the significance of dose selection in terms of the translational utility of the experimental outcome. For example, the results of several studies suggest that repeated treatment with doses of 2.5 mg/kg MP and higher, administered IP, seems to produce locomotor sensitization, whereas repeated daily administration of 1 or 2 mg/kg does not (Gaytan et al 1997, 2000; Kuczenski and Segal 2001; Sripada et al 1998). Furthermore, a lower MP dose (.5 mg/kg), even administered twice daily, did not result in locomotor sensitization either during chronic treatment or in response to a higher stimulant dose challenge (Kuczenski and Segal 2001). It seems, on the basis of these results, that IP doses of 1–2 mg/kg MP are near the threshold for the induction of locomotor sensitization. Importantly, other studies using a variety of measures of potential relevance to consequent drug abuse liability reveal similar threshold effects in this dose range. For example, striatal c-fos expression is enhanced after 2 and 10 mg/kg MP, but not after 1 mg/kg (Chase et al 2003); moderate doses of MP result in suppression of firing of ventral tegmental area dopamine neurons, similar to the effects of AMPH and cocaine, but this effect is minimal at doses around .4–2.0 mg/kg (Brandon et al 2003); and, in a conditioned place preference paradigm, IP administration of MP doses as low as 1.25 mg/kg promoted rewarding effects, but lower doses did not (Meririnne et al 2001). Thus, the relevance of these preclinical observations for the long-term consequences of stimulant treatment of ADHD depends, at least to some extent, on what portion of this dose–response spectrum (.5–5 mg/kg) most accurately reflects

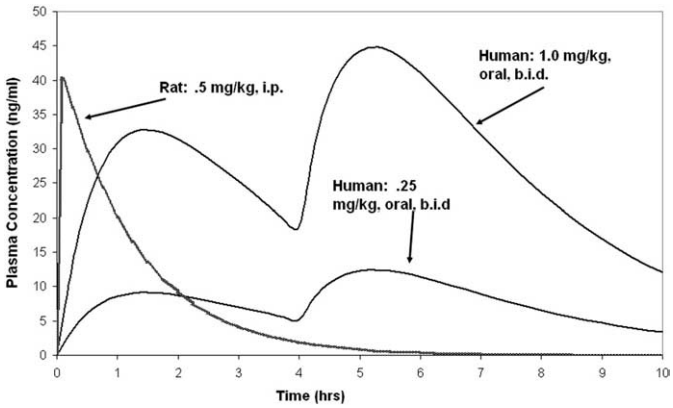

Figure 1. Theoretical plasma concentrations of methylphenidate after oral administration in humans and intraperitoneal administration in rats.