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The effects of methylphenidate on prepulse inhibition during attended and ignored prestimuli among boys with attention-deficit hyperactivity disorder

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Abstract Rationale and objectives: The present study investigated attentional modification of prepulse inhibition of startle among boys with and without attention-deficit hyperactivity disorder (ADHD). Two hypotheses were tested: (1) whether ADHD is associated with diminished prepulse inhibition during attended prestimuli, but not ignored prestimuli, and (2) whether methylphenidate selectively increases prepulse inhibition to attended prestimuli among boys with ADHD. Methods: Participants were 17 boys with ADHD and 14 controls. Participants completed a tone discrimination task in each of two sessions separated by 1 week. ADHD boys were administered methylphenidate (0.3 mg/kg) in one session and placebo in the other session in a randomized, double-blind fashion. During each series of 72 tones (75 dB; half 1200-Hz, half 400-Hz), participants were paid to attend to one pitch and ignore the other. Bilateral eyeblink electromyogram startle responses were recorded in response to acoustic probes (50-ms, 102-dB white noise) presented following the onset of two-thirds of tones, and during one-third of intertrial intervals. Results: Relative to controls, boys with ADHD exhibited diminished prepulse inhibition 120 ms after onset of attended but not ignored prestimuli following placebo administration. Methylphenidate selectively increased prepulse inhibition to attended prestimuli at 120 ms among boys with ADHD to a level comparable to that of controls, who did not receive methylphenidate. Conclusions: These data are consistent with the hypothesis that ADHD involves diminished selective attention and suggest that methylphenidate ameliorates the symptoms of ADHD, at least in part, by altering an early attentional mechanism.

Keywords Attention-deficit hyperactivity disorder · ADHD · Startle reflex · Prepulse inhibition · Methylphenidate · Stimulants

Introduction

Attention-deficit hyperactivity disorder (ADHD) is diagnosed on the basis of problems of inattention and/or hyperactivity-impulsivity [Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, American Psychiatric Association 1994]. Similarly, current theoretical perspectives on ADHD focus on deficits of attention, inhibition, or both. As Douglas (1999) reviews, there is evidence of impairment in a range of cognitive control processes, including sustained attentional allocation. Others have argued against a central attentional deficit in ADHD (Sergeant and van der Meere 1990) and have focused on behavioral inhibition (Quay 1997; Barkley 1999; Sergeant et al. 1999). Despite important differences among these models, all acknowledge that ADHD likely involves poor inhibition. However, neither attention nor inhibition has a single operational definition, and many tasks likely involve elements of both processes (Halperin et al. 1991). Consequently, it has been suggested that investigators choose measures that most simply and directly assess the constructs of interest (Douglas 1999; Sergeant et al. 1999).

Prepulse inhibition of the startle reflex has much to offer in this respect (see the special issue of Psychopharmacology on prepulse inhibition, edited by Koch and Robbins 2001). Prepulse inhibition refers to a decrement in the magnitude of the startle response that occurs when a weak task-irrelevant prestimulus (or prepulse) is presented 60–500 ms before the onset of the startle-eliciting stimulus (for reviews, see Filion et al. 1998; Blumenthal 1999). Prepulse inhibition may reflect a partially automatic mechanism for protecting the initial
processing of sensory stimuli (Graham 1975) or a more general gating mechanism (Braff and Geyer 1990) that serves a critical inhibitory function in sensory, cognitive, and motor output processing.

Furthering its utility as a model system, the brainstem circuitry that mediates prepulse inhibition in the rat is well-known (Fendt et al. 2001). While several neurotransmitter systems regulate prepulse inhibition, the dopaminergic system is predominant in both rat (Swerdlow et al. 2001) and human (Braff et al. 2001) studies. Importantly, striatal dopamine also figures prominently in both the pathophysiology and the treatment of ADHD (Solanto et al. 2001).

Thus, it would seem reasonable to hypothesize that children with ADHD exhibit diminished prepulse inhibition. However, in a large study of boys with and without ADHD, Ornitz and colleagues (1992) found that ADHD was not associated with reduced prepulse inhibition. Similarly, Castellanos et al. (1996) observed diminished prepulse inhibition among boys with Tourette’s Syndrome and ADHD, but not among boys with ADHD only. These studies suggest that ADHD alone is not associated with a deficit in passive prepulse inhibition, which does not require any controlled attentional processing of the experimental stimuli.

However, current perspectives emphasize problems in the allocation of controlled processes in the disorder rather than deficits in automatic processing (Berman et al. 1999; Sergeant et al. 1999). Consistent with this account, Satterfield et al. (1994) reported comparable event-related potentials to ignored stimuli among controls and unmedicated children with ADHD, but children with ADHD exhibited reduced processing of attended stimuli, as evidenced by P300 (see similar findings by Klorman et al. 1994; Jonkman et al. 2000; c.f. Smithee et al. 1998).

Prepulse inhibition can also be used to study controlled attention – active attention to prestimuli increases the degree to which startle is inhibited (DelPezzo and Hoffman 1980). This effect has been most clearly demonstrated in the tone discrimination paradigm of Dawson and colleagues (Dawson et al. 1993; Filion et al. 1993; Schell et al. 1995; Jennings et al. 1996). High- and low-pitched tones, which serve as continuous prestimuli for acoustic startle probes, are presented in an intermixed series. The participant is paid to accurately attend to duration of tones of one pitch but is asked to ignore tones of the other pitch. In this paradigm, prepulse inhibition is evident at various short prepulse-probe stimulus onset asynchronies (SOAs; i.e., 60, 120, and 240 ms) and is greater during attended than ignored tones at 120 ms but not at 60 ms or 240 ms. This enhanced prepulse inhibition to attended prestimuli at the 120-ms SOA is believed to reflect a brief controlled attentional process, perhaps related to confirming the identity of the attended pulse (Dawson et al. 1997). While most of this work has been done with adult participants, attentional modification of prepulse inhibition at a 120-ms SOA was recently replicated in 9- to 12-year-old boys (Hawk et al. 2002a).

The present study tested the hypothesis that unmedicated boys with ADHD, unlike controls, do not exhibit normal attentional modification of prepulse inhibition at 120 ms. It was expected that boys with ADHD would exhibit diminished prepulse inhibition during attended, but not ignored, prestimuli, relative to controls.

The second goal of the present work was to examine the effects of a low dose of methylphenidate on prepulse inhibition among boys with ADHD. Methylphenidate is the most frequently prescribed medication for ADHD (Goldman et al. 1998), and it improves both behavioral and cognitive aspects of the disorder at doses between 0.3 mg/kg and 1.0 mg/kg (Schachar and Ickowicz 1999). Methylphenidate prevents re-uptake of dopamine and norepinephrine, and both actions are believed to be important in the drug’s efficacy (Castellanos 1999; Schachar and Ickowicz 1999; Mehta et al. 2001). From a clinical perspective, methylphenidate would be expected to increase children’s focus on attended tones during the discrimination task, enhancing prepulse inhibition during attended, but not ignored, prestimuli. Indeed, methylphenidate would be expected to reduce prepulse inhibition to ignored prestimuli, both because drugs that increase mesolimbic dopamine availability decrease passive prepulse inhibition (Mansbach et al. 1988; Hutchison and Swift 1999) and because methylphenidate might facilitate ignoring. We tested these hypotheses by examining children with ADHD twice, once following ingestion of 0.3 mg/kg methylphenidate and once following pill placebo, under randomized, double-blind conditions. Comparison of startle modification between medicated boys with ADHD and unmedicated controls allowed a determination of the extent to which methylphenidate normalized prepulse modification. Placebo and methylphenidate were not administered to controls both due to ethical concerns about administering non-therapeutic stimulants to naive normal participants and because previous work with balanced-placebo designs have consistently failed to reveal expectancy effects on methylphenidate’s impact on cognitive, behavioral, or social performance in children with ADHD (Pelham et al. 1997, 2001b, 2002).

Materials and methods

Participants

Participants were 17 boys with a primary diagnosis of ADHD and 14 similarly aged controls. All ADHD and control participants were recruited via a mailing sent to parents of children who had recently participated in a larger study of the effects of methylphenidate. The data for the controls are from a more extensive report that examined startle modification at multiple SOAs, as well as the test-retest reliability of startle modification (Hawk et al. 2002a). In the present study, the primary focus is on ADHD, attentional modification of prepulse inhibition at the 120-ms SOA, and the effects of methylphenidate. However, we have included a subset of previously published control data to allow for more informative comparisons.