D_1 and D_2 dopamine receptor antagonists reverse prepulse inhibition deficits in an animal model of schizophrenia

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Abstract. The amplitude of the acoustic startle response is decreased if the startle stimulus is preceded by a non-startle eliciting stimulus. This sensorimotor gating phenomenon, known as prepulse inhibition, is diminished in schizophrenic individuals. In rats, the dopamine agonist apomorphine disrupts prepulse inhibition and this disruption is reversed by classical and atypical antipsychotics. Furthermore, the ability of antipsychotics to reverse the apomorphine disruption is correlated with clinical potency and D_2 receptor affinity. In the present study, the role of the D_1 receptor in prepulse inhibition of the acoustic startle response was studied; the effects of the D_1 receptor antagonist SCH 23390 were examined and compared to the effects of the D_2 receptor antagonist eticlopride. Male Sprague-Dawley rats were placed into a startle chamber and presented with auditory stimuli consisting of either 95 or 105 dB noise bursts presented alone or preceded by a 75 dB noise burst. Trials consisting of no stimulus and the 75 dB prepulse stimulus alone were also included. These six trial types (ten each) were randomly presented within a 35-min session. Rats treated with 2.0 mg/kg apomorphine (SC) demonstrated a significant disruption of prepulse inhibition compared to vehicle controls. Pretreatment with the D_1 antagonist SCH 23390 (0.01, 0.05, 0.1 mg/kg SC) or the D_2 antagonist eticlopride (0.01, 0.05, 0.1 mg/kg SC) attenuated the disruptive effects of apomorphine. These results indicate that selective blockade of either the D_1 or D_2 receptor subtype is sufficient in reversing the sensorimotor gating deficits produced by apomorphine. The effects of eticlopride and SCH 23390 on prepulse inhibition in saline-treated rats were also examined. Each antagonist produced a dose-related facilitation of prepulse inhibition, suggesting that endogenous DA acting at either receptor subtype plays a role in the tonic modulation of sensorimotor gating.

Key words: Acoustic startle response – Animal model – Apomorphine – Dopamine – Eticlopride – Prepulse inhibition – SCH 23390 – Schizophrenia – Sensorimotor gating – Rats

The amplitude of the acoustic startle response is decreased if the startle stimulus is preceded by a much weaker acoustic or tactile stimulus (Hoffman and Ison 1980). This sensorimotor gating phenomenon, known as prepulse inhibition, appears to be a useful model for studying sensorimotor integration in rodents, and may serve as an animal model of the attentional impairments of schizophrenia (Geyer et al. 1990).

Pharmacological studies suggest that prepulse inhibition is modulated by dopamine (DA) receptors. Systemic injections of the DA agonists apomorphine and amphetamine disrupt prepulse inhibition of the acoustic startle response (Mansbach et al. 1988; Rigdon 1990; Rigdon and Viik 1991; Young et al. 1991) and this disruption is reversed by the DA antagonist haloperidol (Mansbach et al. 1988; Rigdon and Viik 1991). The DA terminal regions that appear to be most important in modulating prepulse inhibition exist in the "limbic" or ventral striatum (Heimer et al. 1985). Thus, microinfusions of DA into the nucleus accumbens or anteromedial striatum, but not the posterolateral striatum or orbital cortex, disrupt prepulse inhibition in rats (Swerdlow et al. 1990, 1992).

Drugs that reverse the disruptive effects of DA agonists on prepulse inhibition are clinically effective in treating schizophrenia (Rigdon and Viik 1991; Swerdlow and Geyer 1992). In fact, the ability of antipsychotics to reverse the apomorphine disruption of prepulse inhibition is correlated with clinical potency and D_2 receptor affinity (Swerdlow and Geyer 1992). These findings, in addition to the observation that prepulse inhibition is reduced in individuals with schizophrenia (Braff et al. 1978, 1992; Grillon et al. 1992), have led to the proposal that the disruption of prepulse inhibition by dopaminergic stimulation represents an animal model of the attent-
Although new receptor subtypes have recently been identified, DA receptors remain classified as two types: D₁-like receptors (D₁, D₃) and D₂-like receptors (D₂, D₂, D₄) (Seeman 1992). Given the importance of prepulse inhibition as both a model for studying the neural substrates underlying schizophrenia as well as a predictive measure for detecting antipsychotics, understanding the relative contribution of DA receptor subtypes in modulating prepulse inhibition has important implications. The results from two studies suggest a critical role for the D₂ receptor family in modulating prepulse inhibition. In a study comparing the effects of D₁ and D₂ selective agonists, it was found that the D₂ agonist quinpirole, but not the D₁ agonist SKF 38393, disrupted prepulse inhibition in drug-naïve rats (Peng et al. 1990). Similarly, when comparing subtype-selective antagonists, the D₁ antagonist SCH 23390, unlike D₂ antagonists, failed to reverse the apomorphine disruption of prepulse inhibition (Swerdlov et al. 1991). Somewhat more recent studies, however, suggest a possible synergistic interaction between D₁ and D₂ receptors. Schwarzkopf et al. (1991) demonstrated an enhancement of prepulse inhibition in saline- or apomorphine-treated rats following the coadministration of haloperidol and SCH 23390, at doses that were ineffective when given alone. A synergistic interaction was also observed when subthreshold doses of subtype selective agonists were combined (Wan and Swerdlov 1993).

The results from the more recent drug interaction studies suggest that D₁ receptors may indeed play an important role in modulating prepulse inhibition. Consequently, we decided to re-evaluate the role of D₁ and D₂ receptor subgroups in prepulse inhibition. In the present series of experiments, the effects of potent and preferentially selective D₁ and D₂ receptor antagonists on prepulse inhibition and on the apomorphine-induced loss of prepulse inhibition were evaluated in rats. The benzazepine derivative SCH 23390 (Iorio et al. 1983) was employed as the preferential D₁ receptor antagonist and the substituted benzamide eticlopride was employed as the preferential D₂ receptor antagonist (Hogberg et al. 1993).

Materials and methods

Subjects. Two hundred and twenty male Sprague Dawley rats (SASCO, St Louis, Mo.) weighing 250–400 g served as subjects. The animals were housed in groups of two or three in a temperature-controlled (2°C ± 1) animal facility on a 12-h light-dark cycle (lights on at 0700 hours) and had free access to food and water. Behavioral testing was conducted between 1300 and 1700 hours.

Apparatus. Startle responses were measured in five rectangular Plexiglas and wire mesh cages (19 x 7.5 x 10.5 cm), each located within a sound-attenuating chamber. Movement of the cage was detected by a piezoelectric transducer placed beneath the cage. Acoustic stimuli were presented by two super tweeters located 10 cm behind the startle cage. One speaker was dedicated to the presentation of background noise (62 dB) while the other speaker delivered the acoustic stimulus. A microcomputer and interface assembly (San Diego Instruments) controlled the presentation of the acoustic stimuli, recorded the startle amplitude, and digitized the amplitude on a scale of 0–4095. Startle amplitude was defined as the difference between the maximum voltage that occurred during 200 ms after the presentation of the acoustic stimulus and the voltage present immediately prior to stimulus onset. The response sensitivities of the five startle cages were calibrated using the method described by Cassella and Davis (1986). This involved placing a 250-g weight on top of a speaker used to vibrate the cage at 10 Hz (the effective frequency of the rat startle response). All five cages had the same response characteristics across a wide dynamic range of the rat’s startle response. Stimulus intensities were measured using a Precision sound level meter (Briel and Kjær). A scale, with the microphone placed inside the startle cage. An impact noise analyzer was built into the sound level meter.

Procedure. Testing for prepulse inhibition occurred over 2 days (separated by 48 h). The first day was a matching day in which prepulse inhibition was measured in drug-free animals; the rats were then assigned to drug groups with each group’s average prepulse inhibition on the match day being equivalent. Thirty-one rats were eliminated because they failed to show robust prepulse inhibition at one of the stimulus intensities (that is, the startle amplitude on prepulse inhibition trials was greater than 80% of the startle amplitude on pulse alone trials). On day 2, the rats were treated with vehicle or 2.0 mg/kg apomorphine and tests for prepulse inhibition were conducted. In additional groups, the effects of eticlopride (0.01, 0.05, 0.1 mg/kg) and SCH 23390 (0.01, 0.05, 0.1 mg/kg) on prepulse inhibition itself and on the blockade of prepulse inhibition induced by apomorphine were tested.

The procedure for measuring prepulse inhibition of the acoustic startle response was the same on each day. Following a 5-min acclimation period with a 62 dB background noise, the rats were presented with ten blocks of six trial types (a total of 60 trials with an inter-trial interval of 30 s). The startle stimuli were 50-ms bursts of 95 or 105 dB white noise. Each of these stimuli was presented alone (pulse alone trials: PA-95 and PA-105) or were preceded 100 ms by a 20-ms burst of 75 dB white noise (prepulse trials: PP-95 and PP-105). Trials consisting of no stimulus and the 75 dB prepulse stimulus alone (prepulse alone trial: PA-75) were also included.

Drugs. SCH 23390 (Research Biochemicals International, Natick, Mass.) was dissolved in distilled water; eticlopride (Research Biochemicals International, Natick, Mass.) was dissolved in 0.98 ml 1% lactic acid, buffered with 0.02 ml 0.1 N NaOH and made up to the appropriate volume with distilled water (final pH: 2.5–3.0). Apomorphine (Sigma, St Louis, Mo.) was dissolved in physiological saline (0.9%) with 0.1% ascorbic acid. All injections were administered subcutaneously in a volume of 1 ml/kg. SCH 23390 and eticlopride were injected 15 min prior to apomorphine. Following the apomorphine injection, the rats were placed immediately into the startle chambers.

Statistical analysis. Prepulse inhibition is presented as percent inhibition of pulse alone startle [(PA–PP/PA) x 100] for each stimulus intensity. A high percentage score indicates a high degree of prepulse inhibition. The prepulse inhibition scores were analyzed using a two-way analysis of variance (ANOVA) (pretreatment dose by treatment). The amplitudes of the acoustic startle responses elicited by the 95 or 105 dB pulse alone stimuli were analyzed using a three-way ANOVA with one repeated measure (stimulus intensity) and two between measures (pretreatment and treatment). A similar analysis was conducted on the no stimulus and 75 dB prepulse stimulus alone trials. Significant interactions were analyzed by tests of simple main effects and appropriate post-hoc comparisons (Fisher’s Least Significant Difference test).

Results

Prepulse inhibition

The mean amplitudes of the acoustic startle responses elicited by the pulse alone and prepulse inhibition trials