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Seroquel (ICI 204,636) restores prepulse inhibition of acoustic startle in apomorphine-treated rats: Similarities to clozapine

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Abstract. Seroquel (ICI 204,636) is a mixed $D_2/5HT_2$ antagonist with a preclinical profile suggestive of potential antipsychotic efficacy. We compared seroquel to clozapine in an animal model of sensorimotor gating deficits in shizophrenic patients. Like schizophrenic patients, rats treated with apomophrine (APO) exhibit deficits in prepulse inhibition (PPI) of acoustic startle. The ability of antipsychotics to restore PPI in APO-treated rats correlates ($R_s = 0.991$) with their clinical potency. Seroquel and clozapine both restore PPI in APO-treated rats. Seroquel's restoration of PPI in apomorphine-treated rats follows simple monotonic ascending dose-response properties, and is not accompanied by consistent changes in startle reflex amplitude. Seroquel's profile in this PPI model mimics that of other antipsychotics.

Key words: Antipsychotic – Apomorphine – Dopamine – Clozapine – Schizophrenia – Startle – Sensorimotor

Seroquel (ICI 204,636; 2-(2-[4-(dibenzo[*b*, *f*][1,4]thiazepin-11-yl)-piperazin-1-yl]ethoxy)ethanol) (Warawa and Migler 1989) is a putative novel antipsychotic with 5-HT_2 and D_2 receptor antagonist properties. Recent reports of the biochemical (Saller and Salama 1993), electrophysiological (Goldstein et al. 1993) and behavioral (Migler et al. 1993) properties of seroquel identify properties similar in many respects to the atypical antipsychotic clozapine, and different from those of typical antipsychotics. In behavioral studies, seroquel and clozapine reversed the locomotor-activating effects of amphetamine in rats, the gaze-shifting effects of apomorphine in cats and the blink-enhancing effects of apomorphine in squirrel monkeys (Migler et al. 1993). While these measures have been used for preclinical screening of antipsychotics, they do not have face or construct validity for any core symptoms of schizophrenia.

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Prepulse inhibition of the acoustic startle reflex has been used in an animal model with face, predictive and construct validity for the sensorimotor gating deficits in schizophrenic patients (Swerdlow et al. 1992, 1994). In humans and rats, the startle reflex is inhibited when the startling stimulus is preceded by 50–500 ms by a weak prepulse, and this prepulse inhibition (PPI) is reduced or eliminated in schizophrenic patients (Braff et al. 1978, 1992) and mesolimbic dopamine (DA)-stimulated rats (Swerdlow et al. 1986, 1990, 1991a). The ability of antipsychotics, including clozapine, to restore PPI in apomorphine-treated rats strongly correlates with their clinical potency ($R = 0.991$) (Swerdlow et al. 1992, 1994; Swerdlow and Geyer 1993). We examined the ability of seroquel to restore PPI in apomorphine-treated rats to extend our understanding of the preclinical profile of this new putative antipsychotic.

Materials and methods

Male Sprague-Dawley rats ($n = 64$; 225–250 g) were housed in groups of two or three and maintained on a reversed 12-h:12-h light/dark schedule (lights off at 0700 h), with food and water provided ad libitum. Behavioral testing occured between 0900 and 1500 h. Animals were handled individually within 3 days of arrival, and daily thereafter.

Behavioral testing began 8–14 days after shipment arrival. Each of four startle chambers (SR-LAB, San Diego Instruments, San Diego, Calif.) was housed in a sound-attenuated room with a 60 dB(A) ambient noise level, and consisted of a Plexiglas cylinder 8.2 cm in diameter resting on a 12.5 × 25.5 cm Plexiglas frame within a ventilated enclosure. Acoustic noise bursts were presented via a speaker mounted 24 cm above the animal. A piezoelectric accelerometer mounted below the Plexiglas frame detected and transduced motion within the cylinder. The delivery of acoustic stimuli was controlled by the SR-LAB microcomputer and interface assembly which also digitized (0–4095), rectified, and recorded stabilimeter readings, with 100, 1 ms readings collected beginning at stimulus onset. Startle amplitude was defined as the average of the 100 readings. Background noise and all acoustic stimuli were delivered through one Radio Shack Supertweeter (frequency reponse predominantly between 5 and 16 KHz) in each chamber. Stimulus intensities and response sensitivities were calibrated to be nearly

identical in each of the four startle chambers (maximum variability <1% of stimulus range and <5% of response ranges). Chambers were also balanced across all experimental groups. Sound levels were measured and calibrated with a Quest Sound Level Meter, A scale (relative to 20 $\mu N/M^2$), with the microphone placed inside the Plexiglas cylinder; response sensitivities were calibrated using an SR-LAB Startle Calibration System.

Three days prior to drug testing, each rat was placed in a startle chamber with 70 dB(A) background noise, and 5 min later was exposed to seventeen 118 dB(A) 40-ms broad band bursts ("PULSE") with a 15-s intertrial interval. Rats were then divided into groups matched for mean amplitude on these trials. Starting 3 days later, rats were tested in two sessions, with 7 days between tests. Seroquel and clozapine were dissolved in half volume 0.1 N HCl and diluted to full volume with saline (final pH 5.0–6.5). Apomorphine was dissolved in saline with 0.1% ascorbic acid. Each rat was pretreated with one dose of either seroquel (0, 2.5, 5.0 or 7.5 mg/kg SC) or clozapine (0 or 7.5 mg/kg IP). Injection volume was 1 mg/ml. Ten minutes later, rats were treated with apomorphine (0 or 0.5 mg/kg SC) and then immediately placed in the startle chambers for a 5-min acclimation period with a 70 dB(A) background noise. After the acclimation period, rats were tested in one of two sessions. One session was designed to study the effects of seroquel on the apomorphine disruption of PPI elicited by relatively intense prepulses. Due to its simple design with a single, relatively intense (15 db(A) above background) prepulse condition, this session is suitable for direct dose-response comparisons, and has been used previously to demonstrate the ability of clozapine and haloperidol to restore PPI in apomorphine-treated rats (Swerdlow and Geyer 1993). In this session, rats ($n=44$) were exposed to two types of stimuli: PULSE, and a prepulse that was 15 dB(A) above background (85 dB(A) 20 ms broad band burst presented 100-ms prior to PULSE). The session included three trial types: PULSE, PULSE preceded by the 15 dB prepulse ("PP15") or no stimulus ("NOSTIM"), presented in pseudorandom order, with a variable intertrial interval (average 15 s). A second session was used to assess the effects of seroquel on PPI over a range of prepulse intensities. In this session, rats ($n=20$) were exposed to four types of stimuli: PULSE, and prepulses that were 3, 5 or 10 dB(A) above background, presented 100 ms prior to PULSE. This session included five trial types: PULSE, PULSE preceded by the 3, 5 or 10 dB prepulse ("PP3, PP5 or PP10", respectively), or NOSTIM, presented in pseudorandom order, with a variable intertrial interval (average 15 s). Previous studies using rat strains, equipment and stimulus parameters similar to the present study have reported no consistent startle-eliciting effects of prepulses (Mansbach et al. 1988). For each session, the testing was repeated 7 days later, but apomorphine doses were reversed, with the number of rats receiving each dose of apomorphine balanced over both weeks.

Each rat was tested in only one session. Startle data were analyzed by mixed design analyses of variance (ANOVAs), with post-hoc Tukey comparisons. PPI was defined as the percent reduction in startle amplitude in the presence of the prepulse compared to the amplitude in the absence of the prepulse [100-(100 × amplitude on prepulse trial/amplitude on PULSE trial)].

FIGURE 1.

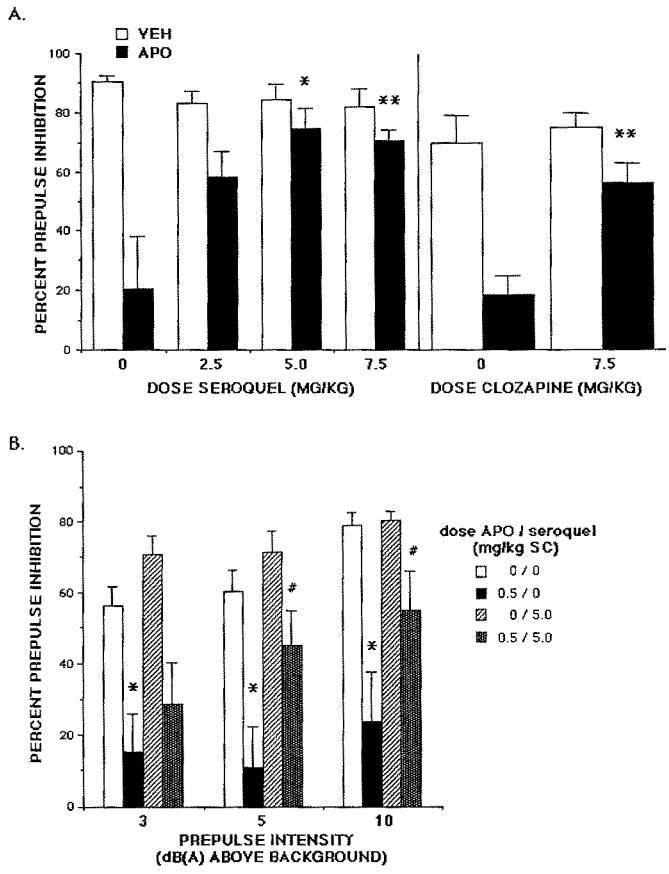

Fig. 1. **A** Effects of seroquel and clozapine on apomorphine disruption of PPI elicited by intense (15 dB over background) prepulses. Significantly greater than 0 mg/kg seroquel in apomorphine-treated rats, * $P<0.05$; ** $P<0.01$. *Right panel*: clozapine reverses the effects of apomorphine on PPI. ** Significantly greater than 0 mg/kg clozapine in apomorphine-treated rats, $P<0.01$. **B** Effects of 5 mg/kg seroquel on apomorphine disruption of PPI elicited by 3, 5 or 10 dB above background prepulses. * Significant effect of apomorphine, and # significant seroquel-induced increase in PPI elicited by 5 and 10 dB prepulses in apomorphine-treated rats, $P<0.05$. There was a near-significant seroquel-induced increase in PPI in rats treated with 0 mg/kg apomorphine, $P<0.1$

Results

Both seroquel and clozapine significantly restored PPI in apomorphine-treated rats. When 15 dB(A) prepulses were used (Fig. 1A, left panel), ANOVA revealed a significant effect of apomorphine ($F=30.70$, df 1,20, $P<0.0001$), no significant effect of seroquel ($F=2.81$, df 3,20, NS), and a significant apomorphine × seroquel interaction ($F=7.18$, df 3,20, $P<0.002$). Post-hoc comparisons revealed that 5.0 mg/kg and 7.5 mg/kg doses of seroquel significantly increased PPI in apomorphine treated rats ($P<0.05$ and $P<0.01$, respectively). In rats treated with 0 mg/kg seroquel, startle levels on prepulse trials were increased by apomorphine from 49.0 ± 16.9 (vehicle) to 324.1 ± 95.7 (0.5 mg/kg apomorphine), while startle amplitudes on PULSE trials were not changed significantly (mean PULSE amplitudes: vehicle = 454.5 ± 86.2 versus 0.5 mg/kg apomorphine = 384.8 ± 29.6). The effect of apomorphine on startle levels on prepulse trials was reversed by seroquel in a dose dependent fashion (324.1 ± 95.7, 216.2 ± 59.9, 55.2 ± 11.4 and 91.1 ± 6.0 for 0, 2.5, 5.0 and 7.5 mg/kg doses, respectively). When clozapine was tested in an identical startle paradigm (Fig. 1A, right panel), ANOVA revealed a significant effect of apomorphine ($F=42.14$, df 1,18, $P<0.0001$), a significant effect of clozapine ($F=6.56$, df 1,18, $P<0.02$), and a significant apomorphine × clozapine interaction ($F=8.96$, df 1,18, $P<0.008$). Post-hoc

comparison revealed that 7.5 mg/kg clozapine significantly increased PPI in apomorphine-treated rats ($P<0.01$). In both seroquel and clozapine experiments, there was no significant effect of order of apomorphine administration (week 1 versus week 2) or interactions of apomorphine order × dose of either seroquel or clozapine ($P>0.05$, all comparisons).

Analysis of startle pulse-alone amplitude revealed that neither seroquel nor clozapine consistently altered startle amplitude. ANOVA revealed a significant effect of seroquel ($F=3.11$, df 1,20, $P=0.05$), a significant effect of apomorphine ($F=5.16$, df 1,20, $P<0.05$), and no significant seroquel × apomorphine interaction ($F=1.36$, df 3,30, NS). Examination of the data revealed that while apomorphine consistently reduced startle amplitude, seroquel tended to increase startle amplitude at the lowest dose (2.5 mg/kg) and reduce startle amplitude at the highest dose (7.5 mg/kg), but neither of these effects of seroquel reached statistical significance. Examination of the effects of clozapine on startle amplitude revealed no significant effect of clozapine ($F<1$) or apomorphine ($F=2.30$, df 1,18, NS) and no clozapine × apomorphine interaction ($F=2.57$, df 1,18, NS).

The lowest dose of seroquel that effectively restored PPI in apomorphine-treated rats was then tested in a paradigm using 3, 5 and 10 dB (A) prepulses. As seen in Fig. 1 B, the effects of seroquel on the apomorphine disruption of PPI vary across the range of prepulse intensities. With more intense prepulses, seroquel restored PPI in apomorphine treated rats, and in all rats, seroquel tended to increase PPI elicited by the weakest (3 dB) prepulses. ANOVA revealed a significant effect of apomorphine ($F=42.26$, df 1,18, $P<0.0001$), a near-significant effect of seroquel ($F=3.56$, df 1,18, $P=0.075$), and no significant apomorphine × seroquel interaction ($F=2.02$, df 1, 18, NS). There was a significant effect of prepulse intensity ($F=10.54$, df 2,36, $P<0.0005$), and a significant interaction of apomorphine × seroquel × prepulse intensity ($F=3.40$, df 2,36, $P<0.05$). Post-hoc comparisons revealed that seroquel significantly increased PPI elicited by more intense (5 and 10 dB) prepulses in apomorphine treated rats ($F=4.58$, df 1,18, $P<0.05$), but not in vehicle-treated rats ($F=1.09$, df 1, 18, NS). When PPI was elicited by weak (3 dB) prepulses, seroquel tended to increase PPI in vehicle-treated rats ($P<0.1$), but not in apomorphine-treated rats ($P>0.1$).

Analysis confirmed that seroquel had no significant effect on startle amplitude. ANOVA revealed no significant effect of seroquel ($F<1$) or apomorphine ($F=2.24$, df 1,18, NS), and no significant seroquel × apomorphine interaction ($F<1$).

Discussion

Our data confirm that seroquel has a preclinical profile suggestive of antipsychotic properties. Thus, like haloperidol, chlorpromazine, perphenazine, prochlorperazine (Swerdlow et al. 1994), spiperone, raclopride (Swerdlow et al. 1991 a), clozapine (Swerdlow et al. 1991 a; Swerdlow and Geyer 1993) and risperidone (Rigdon and Vilk 1991), seroquel restores PPI in apomorphine-treated rats. This effect distinguishes seroquel from many non-antipsychotic psychotropics, including naloxone (Swerdlow et al. 1991 b), propranolol (Swerdlow et al. 1994), imipramine, diazepam and buspirone (Rigdon and Viik 1991), all of which fail to restore PPI in apomorphine-treated rats. The seroquel- and clozapine-restoration of PPI in apomorphine-treated rats cannot be explained by a reversal of an apomorphine-induced loss of prepulse "detection", since apomorphine-treated rats exhibit normal prepulse modulation of reflex latency and thus clearly "detect" the prepulse (cf. Swerdlow et al. 1992). While the relative potency of seroquel versus clozapine was not assessed in this study, data from our previous published studies (Swerdlow and Geyer 1993) using an identical paradigm suggest that seroquel is at least as potent as clozapine, and perhaps slightly more potent than clozapine in restoring PPI. This observation is consistent with existing data in cats and squirrel monkeys (Migler et al. 1993).

In our previous work, clozapine increased baseline PPI when submaximal levels of PPI were elicited by weak (1–5 dB(A)) prepulses (Swerdlow and Geyer 1993). A clozapine-induced increase in PPI was also noted by Hoffman et al. (1993). In the present study, we did not examine the effects of seroquel alone over a full range of weak prepulses, but we did observe a non-significant trend ($P<0.1$) towards a seroquel-induced increase in PPI when 3 dB prepulses were used. In fact, the magnitude of the increase in 3 dB-elicited PPI in rats treated with a "threshold" dose of seroquel (14.4%; present study) is comparable to that produced by a high dose of clozapine (12 mg/kg) in our previous study (17.9%; Swerdlow and Geyer 1993). Whether seroquel shares with clozapine the ability to increase "baseline" sensorimotor gating in rats, independent of the effects of apomorphine or other dopamine agonists, is a focus of ongoing studies.

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