Psychopharmacology (1989) 97:507–513

Psychopharmacology

The role of 5HT1A receptors in the modulation of the acoustic startle reflex in rats

Kevin P. Nanry and Hugh A. Tilson

Laboratory of Molecular and Integrative Neuroscience, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709, USA

Abstract. The modulatory role of serotonin (5-HT) on the acoustic startle reflex was studied using 5-HT receptor agonists and antagonists. 8-Hydroxy-2-(di-*n*-propylamino) tetralin (8-OHDPAT) (1,2 and 4 mg/kg, SC) and 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) (1,2 and 4 mg/kg, IP), putative 5-HT1a receptor agonists, increased the magnitude of the startle reflex, while quipazine (5, 10 and 20 mg/kg, SC), an agonist with mixed 5-HT2 and 5-HT1b receptor activity, decreased startle responsiveness. Pretreatment of rats with ketanserin (1, 2 and 4 mg/kg, SC), a 5-HT2 receptor antagonist, had no significant effect on the activity of 8-OHDPAT, 5-MeODMT, or quipazine. Metergoline (0.25, 0.5, 1 and 2 mg/kg, SC), a mixed 5-HT1/5-HT2 receptor antagonist attenuated the augmentation of the reflex by 8-OHDPAT and 5-MeODMT and the suppression produced by quipazine. At the doses used, metergoline produced a non-dose-dependent increase in startle, while ketanserin had no effect. None of the agents specifically affected the ability of a prepulse stimulus to inhibit the acoustic startle response. These data suggest that 5-HT1a and 5-HT1b receptors play opposite roles in the modulation of the acoustic startle response and that 5-HT plays little, if any, role in the prepulse inhibition of the acoustic startle response.

Key words: Acoustic startle – Prepulse inhibition – Serotonin

The importance of central nervous system 5-hydroxytryptamine (5-HT) in the mediation of sensory-motor responsiveness has been studied extensively (cf. Harvey 1974). Recent research has focused on the observation that 5-HT and related receptor agonists produce a neurological syndrome consisting of head twitching, forepaw treading, tremor, hindlimb abduction, and Straub tail (Jacobs 1976). This 5-HT syndrome appears to be different from the 5-HT-mediated head shake response produced by 5-HT precursors tryptophan or 5-hydroxytryptophan (Corne et al. 1963; Bedard and Pycock 1977; Peroutka 1984) and by 5-HT agonists such as quipazine (Bedard and Pycock 1977).

Recent studies employing radioligand binding techniques have identified four possible 5-HT binding sites in rat brain (Conn and Sanders-Bush 1987). These potential 5-HT receptors have been classified into two major subclasses (5-HT1 and 5-HT2), while there appears to be three receptor subtypes for 5-HT1 (i.e., 5-HT1a, 5-HT1b, 5-HT1c). There have been several attempts to associate 5-HT-mediated behavioral changes with the two major classes of 5-HT receptors. Pharmacological investigations have indicated that the head shake response is associated with activation of 5-HT2 receptors, while the 5-HT syndrome is mediated by the 5-HT1 receptor (Lucki et al. 1984).

Other experiments have implicated 5-HT in the mediation of another sensory-motor response, the acoustic startle reflex. This response is mediated by a relatively simple neural circuit located in the brainstem and spinal cord (Davis et al. 1982). Davis et al. (1980a) reported that infusion of 5-HT intraventricularly to activate forebrain receptors or intrathecally to activate spinal receptors decreased or increased startle responsiveness, respectively. These data support the existence of separate inhibitory and excitatory 5-HT systems located in the forebrain and spinal regions, respectively. This idea is supported by electrophysiological data indicating that 5-HT depresses activity when applied to most forebrain structures (Haigler and Aghajanian 1974), while 5-HT facilitates spinal motoneuron excitability (McCall and Aghajanian 1979; White and Neuman 1980).

Recently, it was reported that the selective 5-HT1a agonist 8-OH-2(di-*n*-propylamino)tetralin (8-OHDPAT) significantly augmented the magnitude of the acoustic startle reflex (Svensson and Ahlenius 1983; Svensson 1985; Davis et al. 1986). Davis et al. (1986) also reported that 1-(*m*-chlorophenyl) piperazine, which has some specificity for the 5-HT1b receptor, decreased startle responsiveness. These data suggest differential functions for the 5-HT1a and 5-HT1b receptor subcasses, at least as it pertains to the startle response.

The purpose of the following study was to investigate in greater detail the role that 5-HT plays in the modulation of the acoustic startle reflex. In these experiments, we used the pharmacological receptor antagonists metergoline, which blocks both 5-HT1 and 5-HT2 receptors, and ketanserin, which has selectivity for 5-HT2 receptors (Leysen et al. 1981) alone and in combination with 5-HT1a agonists 8-OHDPAT and 5-methoxy-N,N-dimethyltryptamine (5-OMeDMT) (Sills et al. 1984) and quipazine, an agonist having effects on both 5-HT1b and 5-HT2 receptors (Martin and Sanders-Bush 1982; Sills et al. 1984). In addition to

Offprint requests to: H. A. Tilson

studying the effects of these agents on the acoustic startle reflex, we also investigated their effects on the prepulse inhibition phenomenon. Presentation of a brief, relatively weak stimulus prior to a stimulus used to elicit the acoustic startle reflex can significantly decrease the magnitude of the startle response (Ison 1984). The neural basis of the prepulse inhibition has not been clearly identified, although it has been reported that lesions in the lateral tegmental area or inferior colliculus reduce the prepulse inhibition phenomenon (Leitner et al. 1981; Leitner and Cohen 1985). Previous work has indicated that pharmacological enhancement of brain 5-HT levels prevented prepulse inhibition (Fechter 1974).

Materials and methods

Subjects. Male, Fischer-344 rats (Charles River Breeding Company, Raleigh, NC) approximately 9–13 weeks of age were housed in plastic home cages with corncob bedding in groups of four. Water and food were continuously available. The animal colony was maintained at a relatively constant temperature ($21 \pm 2°$ C) and relative humidity ($50 \pm 10\%$) with a 12-h light-dark cycle (lights on 0700–1900 hours).

Dosing. The first series of experiments investigated the dose-related effects of the serotonergic drugs on the acoustic startle reflex. In each study, 9–20 rats received either the pharmacological agent or vehicle prior to placement into the testing apparatus. 8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OHDPAT) hydrobromide (Research Biochemicals Inc., Wayland, MA) was dissolved in isotonic saline, vortexed, and injected in doses of 0, 1, 2 or 4 mg/kg, SC. 5 min prior to testing; 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) (Sigma Chemical Co., St Louis, MO) was warmed to 50° C in saline, vortexed, and injected in doses of 0, 1, 2, and 4 mg/kg, IP, 5 min prior to testing. Quipazine maleate (Research Biochemicals Inc.) was dissolved in saline, vortexed, and injected SC in doses of 0, 5, 10, and 20 mg/kg 1 h prior to testing. Three hours prior to testing, rats received SC administration of the two 5-HT antagonists, ketanserin tartrate (Janssen Pharmaceuticals, Beerse, Belgium) and metergoline (Farmitalia, Milan, Italy). Ketanserin was dissolved in saline, vortexed, and given in doses of 0, 1, 2 and 4 mg/kg, while metergoline suspended in an aqueous solution of Tween-80 (2 drops per 10 ml saline) and given in doses of 0, 0.25, 0.5, 1 and 2 mg/kg). Behavioral data from the Tween-80 vehicle control did not differ significantly from the other vehicle control groups. In a second series of experiments, the effects of these agents on prepulse inhibition were studied using the same dosing parameters. Doses were calculated on the basis of the salt.

The third set of experiments concerned the interaction between the serotonergic agonists and antagonists using the acoustic startle response as the indicator of pharmacological activity. In these experiments, ketanserin and metergoline were given in doses of 2 and 0.5 mg/kg, respectively, SC, 3 h prior to testing. 8-OHDPAT (1 and 4 mg/kg, SC) and 5MeODMT (4 mg/kg, IP) were given 5 min prior to testing, while quipazine (2.5 and 10 mg/kg, SC) was given 1 h prior to testing. Doses and treatment times for all experiments were based upon pilot data and reports from other laboratories (Davis and Sheard 1974; Samanin et al. 1976; Svensson and Ahlenius 1983; Lucki et al. 1984; Svensson 1985).

Acoustic startle response. Rats were tested in an apparatus described in detail by Herr et al. (1987). Briefly, the animals were placed in small acrylic cages ($13.5 \times 25 \times 9$ cm) suspended 1 mm above a platform attached to a load cell assembly. The test cage was located inside a sound and light attenuating acoustical chamber (Model AC-2, Industrial Acoustic Co., Bronx, NY). The rats were given 20 trials of a 110 dB, 200 ms, 8 kHz tone from a speaker suspended 27.5 mm above the test cage. The magnitude of the startle response was quantified by a peak hold circuit which measured the most intense response occurring over the first 100-ms period after each stimulus presentation. A PDP-8A minicomputer using Super-Sked software performed the analog/digital transformations of the transducer output.

The startle response apparatus described above was used to measure pharmacological alterations in prepulse inhibition. In these experiments, rats received 36 trials per session as described in detail elsewhere (Saitoh et al. 1986, 1987). The intertrial interval varied from 28 to 52 s and averaged 39 s. There were six trials in each of six conditions in which a 20 ms pulse of white noise (70 dB) preceded a tone of the same duration by 0, 0.01, 0.04, 0.08, 0.1 or 4 s measured from the offset of the noise of the onset of the tone (i.e., interstimulus interval, ISI). The order of presentation of the ISIs was determined by a 6×6 latin square design. In trials with an ISI of 0 s, white noise was not presented and is defined as the control trial. After calculating the magnitude (V) of the startle response for each of the 6 ISI conditions, the maximum reduction of the startle reflex magnitude was calculated for each animal by subtracting the lowest average voltage at any ISI from that recorded for the control trial.

Statistical analyses. The data from the dose-response experiments were analyzed for overall treatment effects using a one-way analysis of variance (ANOVA) (Winer 1971). If data were transformed to percent of control, ANOVA was performed on the transformed data. If a significant overall effect was observed, comparisons between means were made using Fisher's Least Significant Difference Test (Miller 1966). In the drug interaction studies, a two-way ANOVA was used to determine significant interactions between antagonists and agonists. The accepted level of significance was $P < 0.05$.

Results

Dose-response effects

Acoustic startle. In order to facilitate comparisons between the several experiments, data are presented as the per cent change from each respective vehicle control. Figure 1 shows that 8-OHDPAT significantly increased startle responsiveness [$F(3,46) = 26.19$, $P < 0.01$]; post hoc tests showed that the increase was seen at all of the doses tested. 5-MeODMT also significantly elevated the magnitude of the startle response [$F(3,46) = 14.00$, $P < 0.01$]. Post hoc comparisons showed that only the highest dose (4 mg/kg) was effective. Quipazine also had a significant effect on the acoustic startle response [$F(3,46) = 6.54$, $P < 0.01$]. However, in contrast to 8-OHDPAT and 5-MeODMT, the two lower doses of quipazine (5 and 10 mg/kg) decreased startle response magnitude. The highest dose (20 mg/kg) had no significant effect on the magnitude of the startle response.

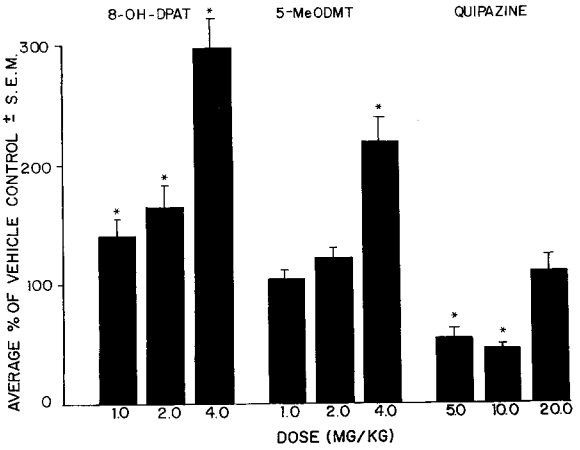

Fig. 1. The effects of serotonergic agonists 8-OHDPAT, 5-MeODMT and quipazine on the magnitude of the acoustic startle reflex. Data are average per cent of vehicle control for each compound ±SE of the mean of nine to ten rats per group. The vehicle control groups had 20 rats per group and their control values were 1.2±0.2, 1.1±0.1 and 1.2±0.2 V per trial for 8-OHDPAT, 5-MeODMT and quipazine, respectively. The *asterisks* indicate a significant difference from vehicle control ($P<0.05$, Fisher's LSD following significant ANOVA for treatment)

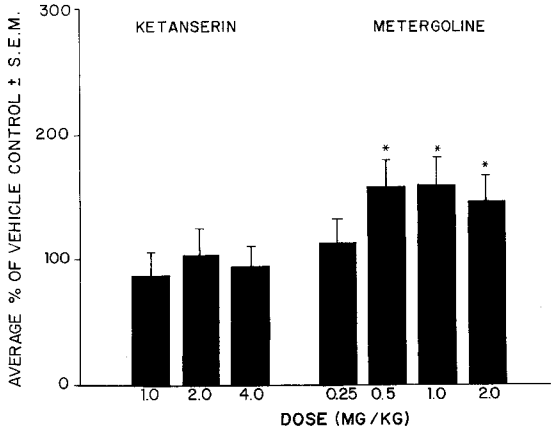

Fig. 2. Effects of serotonergic antagonists ketanserin and metergoline on startle responsiveness. Data are average per cent of vehicle control ±SE for eight to ten rats in each experimental group. The vehicle control means were 1.1±0.1 and 1.0±0.1 V for the ketanserin and metergoline experiments, respectively. There were 20 and 18 rats in the control groups for ketanserin and metergoline, respectively. The *asterisks* indicate a significant difference from vehicle control ($P<0.05$, Fisher's LSD following significant ANOVA for treatment)

Figure 2 shows that at the doses tested, the 5-HT2 antagonist ketanserin had no significant effect on startle reactivity ($F=0.14$). One-way ANOVA indicated that the mixed 5-HT1 and 5-HT2 antagonist metergoline had a significant effect on the startle response [$F(4,48)=2.78$, $P<0.05$]. Post-hoc tests indicated that 0.5, 1 and 2 mg/kg significantly increased the startle response. The lowest dose of metergoline tested (0.25 mg/kg) was without effect.

Prepulse inhibition. Figure 3 shows that 8-OHDPAT had a significant effect on magnitude reduction [$F(3,46)=3.31$, $P<0.05$]. Post hoc comparisons indicated significant differences between the control group and animals receiving 1 or 4 mg/kg 8-OHDPAT. However, these differences were attributed to the observation that 8-OHDPAT elevated the response at the 0 ISI, without increasing the magnitude of the response at other intervals (Table 1). One-way ANOVA indicated no significant overall effect of 5-MeODMT on prepulse inhibition [$F(3,46)=2.28$, $P>0.05$], while quipazine had a significant effect on this measure [$F(3,46)=4.21$, $P<0.025$]. Significant alterations in magnitude reduction were observed following 5 and 10 mg/kg quipazine. However, this effect was attributed to the observation that 5 and 10 mg/kg decreased responsiveness at the control without affecting responsiveness at the other ISIs. Table 1 shows that changes in magnitude reduction are highly associated with decreases in responsiveness at the control ISI.

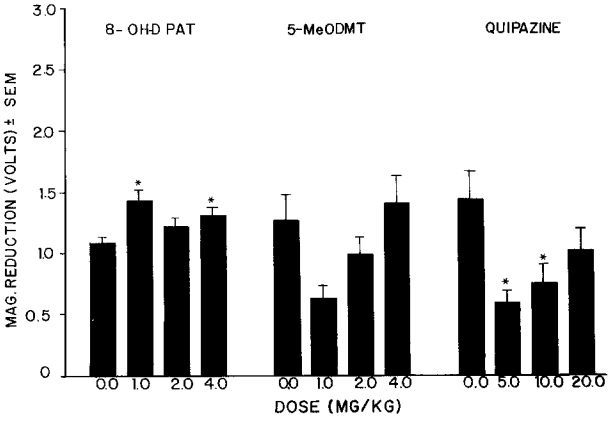

Fig. 3. Effects of serotonergic receptor agonists 8-OHDPAT, 5-MeODMT and quipazine on prepulse inhibition of acoustic startle of rats. The data are average maximum magnitude reduction values (V) ±SE of ten rats per group. There were 20 rats in each control group. The *asterisk* indicates a significant difference from vehicle control ($P<0.05$, Fisher's LSD following ANOVA for overall significance)

Figure 4 shows that at the doses tested ketanserin had no significant effect on prepulse-induced magnitude reduction [$F(3,46)=1.96$, $P>0.10$]. One-way ANOVA indicated that metergoline had a significant effect on magnitude reduction [$F(4,49)=2.92$, $P<0.05$]. Post hoc comparisons found significant alterations following 0.25 and 2 mg/kg metergoline. In the case of the higher dose (2 mg/kg), the increase in magnitude reduction could be attributed to an increased responsiveness at the control ISI without effect on responsiveness at the other ISIs (Table 1).

Pharmacological interactions

Acoustic startle response. A two-way ANOVA showed a significant interaction between 8-OHDPAT and metergoline [$F(2,54)=3.47$, $P<0.05$] and post hoc comparisons showed that metergoline significantly decreased the responsiveness produced by both 1 and 4 mg/kg 8-OHDPAT (Fig. 5). There was no significant interaction between ketanserin and 8-OHDPAT [$F(2,54)=1.18$, $P>0.10$]. Figure 5 also shows that the interaction between 5-MeODMT and metergoline was significant [$F(1,36)=5.70$, $P<0.05$] and post hoc comparisons found that the mean of the animals

Table 1. Effects of serotonergic agents on response at the control ISI

Compound (mg/kg)		*N*	Average voltage ± SE
8-OHDPAT	0	20	1.7 ± 0.1
	1	10	2.7 ± 0.3[a]
	2	10	2.0 ± 0.2
	4	10	2.7 ± 0.2[a]
5-MeODMT	0	20	1.7 ± 0.2
	1	10	1.0 ± 0.1[a]
	2	10	1.4 ± 0.2
	4	10	1.8 ± 0.2
Quipazine	0	20	1.8 ± 0.2
	5	10	1.2 ± 0.2[a]
	10	10	1.3 ± 0.2[a]
	20	10	1.4 ± 0.2
Ketanserin	0	20	0.8 ± 0.1
	1	10	1.0 ± 0.1
	2	10	1.0 ± 0.3
	4	10	1.4 ± 0.3
Metergoline	0	19	0.8 ± 1.1
	0.25	9	1.2 ± 0.2
	0.50	9	0.9 ± 1.2
	1	9	1.2 ± 0.3
	2	8	1.5 ± 0.2[a]

[a] Differs significantly from control group

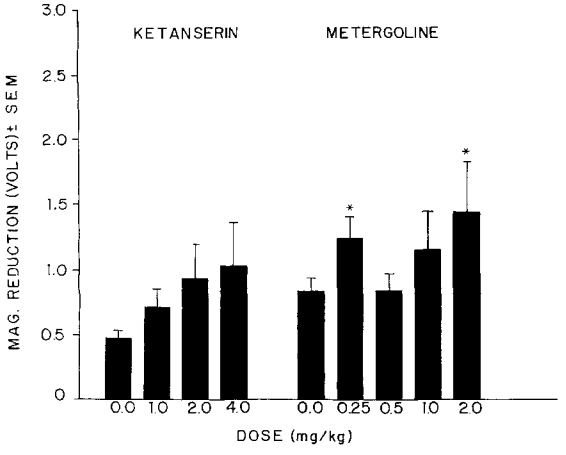

Fig. 4. Effects of serotonergic receptor antagonists ketanserin and metergoline on prepulse inhibition of the acoustic startle response. The data are average maximum magnitude reduction values (V) ± SE of eight to ten rats per experimental group. There were 19–20 rats in the vehicle control groups. The asterisks indicate a significant difference from vehicle control ($P < 0.05$, Fisher's LSD following significant overall ANOVA)

receiving metergoline and 5-MeODMT was significantly lower than that of animals receiving 5-MeODMT only. ANOVA showed that the interaction between 5-MeODMT and ketanserin was not significant [$F(1,36) = 3.24$, $P > 0.05$]. Metergoline interacted significantly with quipazine ($F(2,54) = 4.54$, $P < 0.05$], while there was no significant interaction between ketanserin and quipazine [$F(2,54) = 2.20$, $P > 0.10$]. Post hoc comparisons found that the responsiveness of rats receiving both metergoline and either 2.5 or 10 mg/kg quipazine was significantly greater than rats receiving either dose of quipazine alone.

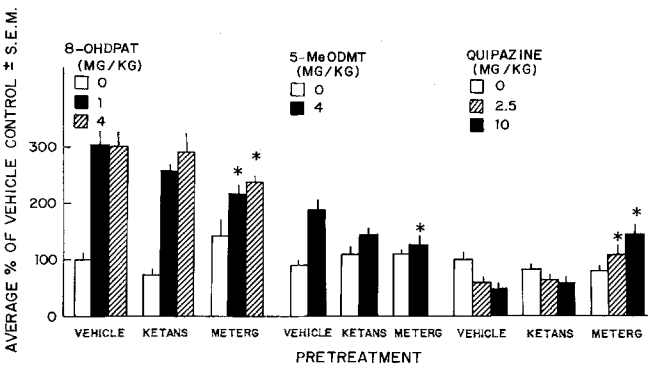

Fig. 5. Effects of pretreatment with serotonergic antagonists, ketanserin (2 mg/kg) and metergoline (0.5 mg/kg) on alterations in startle responsiveness produced by 8-OHDPAT, 5-MeODMT and quipazine. The data are average change from control values (V) ± SE of ten rats per experimental group. The control values were 0.8 ± 0.1, 1.5 ± 0.3 and 1.3 ± 0.3 V for the 8-OHDPAT, 5-MeODMT and quipazine experiments, respectively. There were ten rats per control group. The *asterisks* indicate a significant difference in response in antagonist-treated groups relative to receptor agonist only ($P < 0.05$, Fisher's LSD after significant interaction determined by ANOVA)

Discussion

The results of the present experiments support previous conclusions that serotonin (5-HT)-containing systems play a modulatory role in the mediation of the acoustic startle reflex (Davis et al. 1980a, 1986). Our data also support findings indicating that 5-HT1a receptors play a facilitative role in the startle reflex. Like other laboratories (Svensson and Ahlenius 1983; Svennson 1985; Davis et al. 1986), we observed that 8-OHDPAT increased the magnitude of the acoustic startle reflex; 8-OHDPAT has been report to be a specific 5-HT1a receptor subtype agonist (Middlemiss and Fozard 1983; Peroutka 1985). In addition, we observed that 5-MeODMT, a relatively selective 5-HT1a receptor agonist (Sills et al. 1984), also increased the magnitude of the acoustic startle response, an observation made previously by Davis and colleagues (Davis et al. 1980b, 1986; Commissaris and Davis 1982).

The conclusion that the facilitative effects of 8-OHDPAT and 5-MeODMT on startle responsiveness are mediated by the 5-HT1 receptor receives additional support from our observation that pretreatment with metergoline attenuated the effects of both 8-OHDPAT and 5-MeODMT. Metergoline has been reported to have a high affinity for both 5-HT1a and 5-HT1b receptor subtypes (Sills et al. 1984) and 5-HT2 receptors (Leysen et al. 1981). Ketanserin, which has a high affinity for only 5-HT2 receptors (Leysen et al. 1981), had no significant effect on the enhancement of the acoustic startle produced by either 8-OHDPAT or 5-MeODMT. These data are also in accord with those of Davis (1987), who reported that ketanserin attenuated the facilitative effects of mescaline, and effect believed to be mediated by the 5-HT2 receptor. Davis et al. (1986) have also reported that cyproheptadine, a mixed receptor antagonist (Sills et al. 1984), attenuated the excitatory effects of 5-MeODMT.

Our finding that metergoline attenuated the behavioral effects of 8-OHDPAT is not in accord with those of Svennson (1985), who reported that methiothepin, but not meter-

goline, blocked the effect of 8-OHDPAT on the acoustic startle response. Hjorth et al. (1982) have also reported that methiothepin, but not metergoline, antagonized 8-OHDPAT-induced stereotypic motor movements. On the other hand, Blackburn et al. (1984) reported that 8-OHDPAT-induced rotational behavior in animals with 5,7-dihydroxytryptamine (5,7-DHT) lesions of the dorsal raphe nucleus was blocked by metergoline, but selective 5-HT2 receptor antagonists ketanserin and pirenperone were not effective. This rotational behavior in 5,7-DHT-lesioned rats appears to be mediated by the 5-HT1a receptor, since similar effects are seen with 5-MeODMT and RU-24969, but not after quipazine (Blackburn et al. 1984). Finally, the functional significance of the finding that methiothepin, but not metergoline, antagonized 8-OHDPAT (Svensson 1985) is not clear, since it is known that methiothepin has significant dopaminergic and noradrenergic receptor antagonistic properties (Lloyd and Bartholini 1974). Furthermore, other studies have found that methiothepin, like ketanserin and other agents having little or no specificity for the 5-HT1a receptor, failed to block the discriminative stimulus properties of 8-OHDPAT (Tricklebank et al. 1987). Clearly, additional work will be needed to clarify the role that the 5-HT1a receptor plays in the enhancement of startle reactivity produced by 8-OHDPAT.

The results of the present experiments also indicate that quipazine significantly decreases acoustic startle reactivity. Previously, it has been reported that quipazine produces a number of effects in vivo believed to be due to the activation of central 5-HT receptors, including head-twitching (Malick et al. 1977; Lucki et al. 1984), antinociception (Samanin et al. 1976), neuroendocrine alterations (Meltzer et al. 1976; Fuller et al. 1978), decreased food intake (Samanin et al. 1977), alterations in food-reinforced operant behavior (Mokler et al. 1983) and decreased brain 5-HT turnover (Grabowska et al. 1974; Green et al. 1976). Lucki et al. (1984) have reported that the head-twitch response produced by quipazine is mediated by the 5-HT2 receptor, since it is blocked by 5-HT2 receptor antagonists such as ketanserin.

Our data suggest that the quipazine-induced decrease in startle reactivity is not due to activation of 5-HT2 receptors, since ketanserin did not attenuate the effects of quipazine. Subsequent work verified that head twitching induced by 2.5 and 5 mg/kg quipazine could be blocked by pretreatment with a similar dose and predosing time of ketanserin (Fig. 6). However, the effects of 10 mg/kg quipazine were not blocked by ketanserin when given 3 h prior to testing. A subsequent experiment found that if ketanserin (2 mg/kg) and quipazine (10 mg/kg) were administered at the same time and testing occurred 1 h later, ketanserin attenuated but did not block quipazine-induced head-twitching (quipazine = 9.3 ± 1.0 responses/15 min ± SE; quipazine + ketanserin = 5.3 ± 0.9 responses (15 min ± SE). Finally, we have observed that 2 mg/kg ketanserin did not attenuate suppression of startle produced by 2.5 mg/kg quipazine when testing occurred 1 h after dosing with either drug (quipazine = 0.65 V ± 0.07; quipazine + ketanserin = 0.63 V ± 0.08).

Quipazine-induced suppression of startle reactivity was affected significantly by metergoline, which has both 5-HT1 and 5-HT2 receptor antagonistic properties (Lucki et al. 1984). One interpretation of these data is that the behavioral effect of quipazine observed in the present experiment is due to its activity on 5-HT1b receptors. Sills et al. (1984)

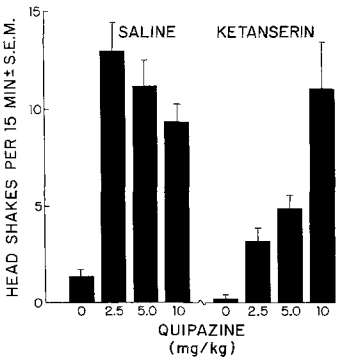

Fig. 6. Effects of ketanserin pretreatment on quipazine-induced head twitching in rats. Animals were dosed with 2 mg/kg ketanserin 2 h prior to 2.5, 5 or 10 mg/kg quipazine. Testing occurred 1 h later. There were eight rats per group and rats were observed for head twitching for a 15-min period. Quipazine produced significant increases in the rate of head twitching at 2.5, 5 and 10 mg/kg. Ketanserin significantly blocked the effect at 2.5 and 5 mg/kg quipazine

reported that quipazine and 1-(*m*-chlorophenyl)piperazine (*m*CPP) are selective for the 5-HT1b receptor; Davis et al. (1986) recently reported that *m*CPP significantly decreased startle reactivity in rats. These data suggest that activation of 5-HT1a and 5-HT1b receptors can have opposite effects on some behavioral endpoints.

The results of the present work do not indicate a major role for 5-HT in the mediation of the prepulse inhibition phenomenon. It has been postulated that there is an inhibitory pathway parallel to the startle reflex arc in the brainstem (Hoffman and Ison 1980) and recent work in our laboratory supports the conclusion that the circuit may begin at the level of the lateral lemniscus in the brainstem (Saitoh et al. 1987). Fechter (1974) reported that elevation of 5-HT levels by administration of its precursor 5-hydroxytryptophan and a monoamine oxidase inhibitor, pargyline, resulted in a significant increase in the magnitude of the startle response on control trials (i.e., 0 s ISI) and a diminution in the degree of response inhibition produced by the prepulse stimulus. In our experiments using pharmacological receptor agonists, we observed increases (8-OHDPAT and 5-MeODMT) or decreases (quipazine) in the magnitude of the startle response at the control ISI. However, we did not observe significant drug-induced changes in the ability of the animals to inhibit startle reactivity to the prepulse stimulus, at least at the doses of 8-OHDPAT, 5-MeODMT and quipazine used in these studies. Saitoh et al. (1986) reported that pretreatment with phenoxybenzamine, an alpha-adrenergic receptor blocker, also significantly modified responsiveness at the control ISI without affecting responsiveness at the other ISIs. These data suggest that descending monoaminergic pathways may have little modulatory influence on the ability to inhibit responsiveness to acoustic stimulation.

The data from this study emphasize the importance of the serotonergic system in the expression of the acoustic startle reflex. 5-HT receptors, possibly of the 5-HT1a subtype, appear to play a facilitative role in the modulation of startle, while 5-HT2 receptors play a suppressive role. The 5-HT system does not appear to play a major modulatory role in the prepulse inhibition of the acoustic startle reflex. Additional work is needed to elucidate the precise

anatomical localization of the 5-HT receptors and the functional interaction between the various receptor subtypes involved in the acoustic startle response.

Acknowledgements. The technical assistance of Mr Charles Hamm and Robert Hall in performing these experiments and the typing and editorial assistance of Mrs. Loretta Moore is gratefully acknowledged. The authors are also grateful to Drs. James Ison and John Foss of the University of Rochester for the use of their computer software.

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Received August 5, 1988 / Final version October 11, 1988