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Effects of 8-OH-DPAT, Lisuride and some ergot-related compounds on the acoustic startle response in the rat

Lennart Svensson

Department of Psychology, University of Göteborg, P.O. Box 14158, S-400 20 Göteborg, Sweden

Abstract. Five ergot-related compounds were examined for their effects on the acoustic startle response in the rat. The startle amplitude and the startle latency were registered. 8-Hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT; 0.5–8 mg/kg) and lisuride (0.05–0.8 mg/kg) were found to enhance the startle amplitude, while the mainly DA receptor active ergot derivatives pergolide (0.2–0.8 mg/kg), bromocriptine (5–20 mg/kg) and LY 141865 (5–20 mg/kg) had no, or even the reverse, effect. All five compounds caused a prolongation of the startle latency. The increased startle amplitude caused by 8-OH-DPAT (2 mg/kg) and lisuride (0.2 mg/kg) was successfully antagonized by the 5-HT receptor antagonist methiothepin (0.1 mg/kg) but not by metergoline (1 mg/kg). 5-Hydroxy-L-tryptophan (L-5-HTP; 12.5–50 mg/kg), administered to pargyline- and benserazide-pretreated animals, was included for comparison. The serotonin precursor caused a marked increase in the startle amplitude and a shortening of the startle latency.

Key words: 8-OH-DPAT – Lisuride – Ergot derivatives – Acoustic startle – Rat

The serotonergic (5-HT) and the dopaminergic (DA) neuronal systems in the CNS are believed to be involved in processes which excitate the acoustic startle response in the rat (cf Davis 1980). Thus, it seems that an increase in 5-HT transmission enhances startle. 5-HTP administered to benserazide-, or more noticeably, benserazide- and pargyline-pretreated animals increases the response (Fechter 1974a; Svensson and Ahlenius 1983). Furthermore the proposed 5-HT receptor agonist 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) increases acoustic startle. This effect is blocked by the putative 5-HT receptor antagonists cinanserin or cyproheptadine (Davis et al. 1980a).

DA-receptor agonists also seem to exert an excitatory effect on startle. The well-known DA receptor agonist apomorphine causes an increase in acoustic startle, which is blocked by the putative DA antagonists haloperidol or pimozide (Davis and Aghajanian 1976). An increased startle response is also induced with high doses of amphetamine, and these effects are also blocked by pimozide (Kehne and Sorenson 1978). However, administration of L-dopa has little effect on acoustic startle (Fechter 1974b; Svensson and Ahlenius 1983), even though a significant increase in startle has been achieved in mice at higher doses (Kokkinidis and MacNeill 1982), and in general the effect on startle caused by manipulation of DA mechanisms seems to be less impressive compared to those obtained by manipulation of 5-HT mechanisms. Thus, it has been questioned whether the DA system exerts a tonic excitatory effect on startle or not (Davis 1980).

Many ergot alkaloides and ergot related compounds are known to interfere with the 5-HT or DA neuronal transmission, thus providing additional tools to evaluate the nature of startle behaviour. In a recent study we showed that the ergot congener 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), a putative 5-HT receptor agonist (Arvidsson et al. 1981; Hjorth et al. 1982), had a marked stimulatory effect on acoustic startle in the rat (Svensson and Ahlenius 1983). This study was extended, and in addition to 8-OH-DPAT, four other ergot related compounds with proposed agonistic effects on central 5-HT and/or DA receptors were examined. It would be expected that if 8-OH-DPAT exerts its behavioural effects via an activation of 5-HT receptors, these effects should resemble those caused by an endogenous increase in 5-HT transmission. Therefore 5-HTP administered to pargyline- and benserazide-pretreated animals was included in the study. Furthermore the behavioral effects of 8-OH-DPAT should be sensitive to 5-HT antagonists. In order to evaluate this aspect, the putative 5-HT receptor antagonists methiothepin (Lloyd and Bartholini 1974) and metergoline (Fuxe et al. 1975b) were examined for their antagonistic effect on the 8-OH-DPAT-induced increase in startle.

Methods

Animals. Male Sprague-Dawley rats (Anticimex, Sollentuna, Sweden), 320–350 g, were used. The animals were housed three per cage in constant temperature and humidity with food and water constantly available. The day-light cycle was artificially maintained (dark 11.00 a.m.–11.00 p.m.).

Drugs. 8-Hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) hydrobromide (obtained from the Organic Chemistry Unit, Department of Pharmacology, University of Göteborg, Göteborg, Sweden), lisuride hydrogen maleat* (Schering AG, Berlin, FRG), 5-hydroxy-L-tryptophan (L-5-HTP; Fluka AG, Buchs, Switzerland), pergolide mesylate* (Eli Lilly & Co, Indianapolis, Indiana), bromocriptine mesilate* (Sandoz Ltd, Basel, Switzerland), LY 141865 dihydrochloride* (Eli Lilly & Co, Indianapolis, Indiana), pargyline hydrochloride (Abbott, Scandinavia AB, Spånga, Sweden), benserazide hydrochloride and

methiothepin* (Hoffman-La Roche, Basel, Switzerland), metergoline (Farmitalia, Milan, Italy). Pergolide was dissolved in a few drops of glacial acetic acid and final volume made up with 0.9% saline solution, bromocriptine in a few drops of 70% alcohol and final volume made up with distilled water, metergoline in a few drops of glacial acetic acid and final volume made up with 5.5% glucose. All other drugs were dissolved in 0.9% saline. Controls were given the respective vehicles. Acidity was adjusted with sodium hydroxide when necessary. Pergolide and bromocriptine were injected subcutaneously (SC), the other drugs intraperitoneally (IP), in a volume of 2 ml/kg. The doses refer to the forms indicated above.

Apparatus. A plexiglas cage (16 × 15 × 8.5 cm) with a freely moving bottom suspended under the cage by rubber bands was used to register the amplitude of the startle response. An accelerometer (Entran Devices EGAL-125-10D) with the voltage output proportional to the velocity of displacement was attached to the bottom. The accelerometer was connected to a voltage peak detector, and startle amplitude was registered as the maximum accelerometer voltage that occurred during the first 200 ms after the startle stimulus was delivered. The startle latency was registered as the time between onset of the acoustic startle stimulus and the occurrence of the first positive response-elicited voltage exceeding a preset value in a startle threshold circuit. A schematic drawing of the recording apparatus and the typical accelerometer output is shown in Fig. 1. The acoustic startle stimulus consisted of a 100-ms 100-dB (A) burst of white noise which was delivered to the animal by a high-frequency speaker built into the top of the cage. The cage was placed in a dimly lit, sound-attenuated box (72 × 64 × 48 cm). Sound level was measured inside the cage by means of a sound level meter (Brüel and Kjaer 2206 with microphone cartridge 4148). Background noise level was 38 dB (A) and consisted of residual amplifier noise.

Experimental procedure. One week after delivery by the breeder all animals were subjected to a startle pretest. Following saline injections the animals were placed in the startle cage for 10 min and thereafter given a series of 100 db (A) noise bursts every 10 s for 20 trials. This was also the testing schedule in the experiments. The animals were then tested every 3rd or 4th day in a balanced design, each

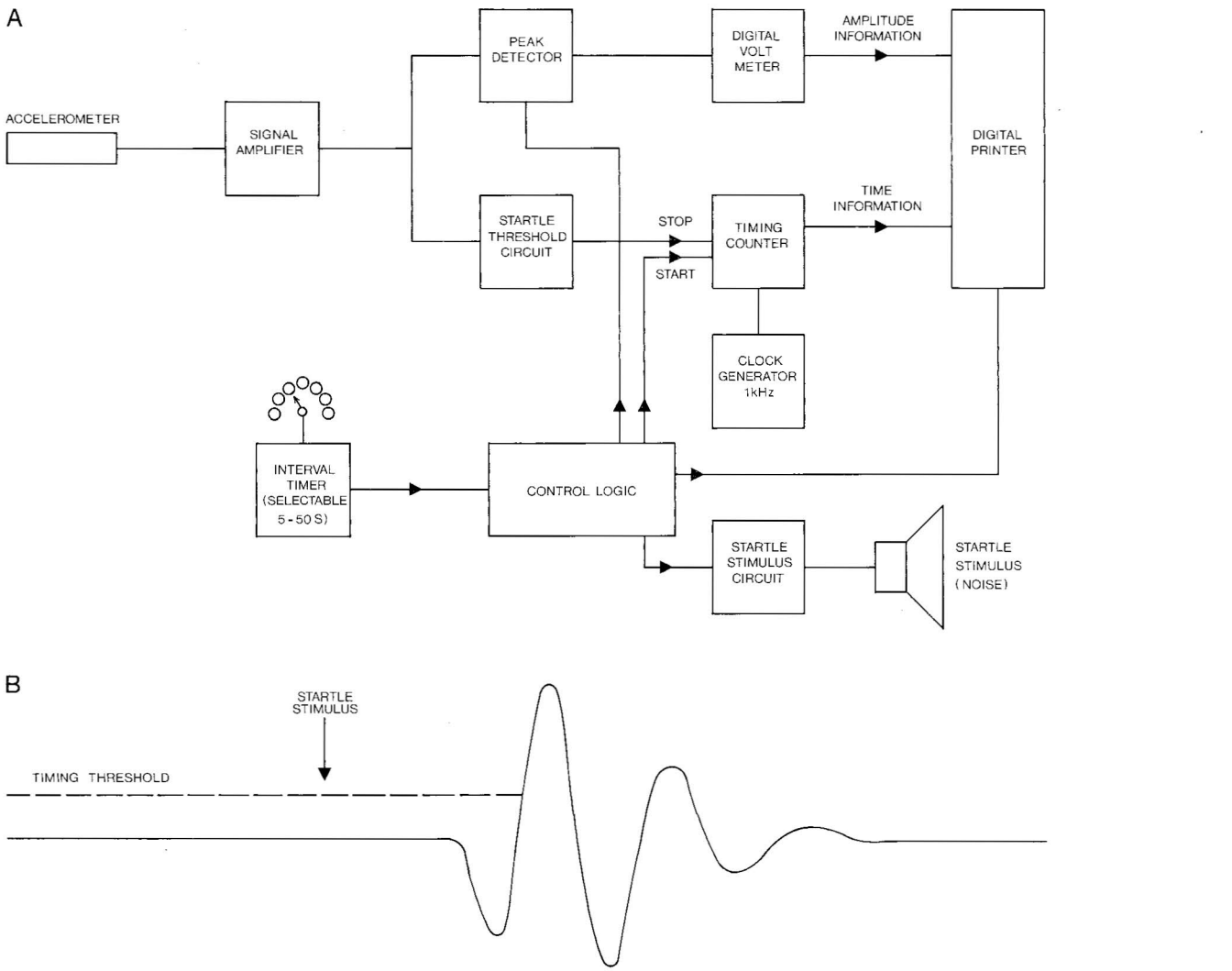

Fig. 1. Schematic drawing of the startle response recording apparatus used in the experiments (**A**), and the typical voltage output of the accelerometer (**B**)

animal given all doses of the drug, saline included. In the 5-HTP experiment, however, the animals were tested only once. Some test series were randomly selected and controls statistically tested for day effects (Kruskal-Wallis one-way ANOVA). No significant effects were found.

Statistics. The mean startle amplitude and the mean startle latency were calculated for each animal in each session and used as the data in the statistical analysis. The data were analysed by means of Friedman two-way ANOVA followed by Wilcoxon matched-pairs signed-ranks test (Wilcoxon *t*-test) or Kruskal-Wallis one-way ANOVA followed by Mann-Whitney *u*-test (Siegel 1956). Recorded startle latencies shorter than 15 ms or longer than 50 ms were considered as artefacts and excluded from the statistical analysis. Animals which achieved less than five approved startle latencies in a single test were left out. Two-tailed levels of significance were used and $P > 0.05$ was considered as non-significant. The results are represented by the averaged mean and standard error of the mean (SEM) in the figures.

Results

Effects of five ergot-related compounds on the acoustic startle response

8-OH-DPAT. The animals showed a dose-dependent increase in the averaged amplitude of the startle response ($P < 0.001$, Friedman two-way ANOVA; Fig. 2), the increase being statistically significant from 0.5 to 8 mg/kg. The startle latency was also increased ($P < 0.01$, Friedman two-way ANOVA), but individual comparisons reveal that the increase was significant only at 8 mg/kg. The animals showed a pronounced 5-HT syndrome consisting of flat body posture, forepaw extension and treading, abducted hindlimbs and straub tail. Profuse salivation occurred at higher doses.

Lisuride. The administration of lisuride caused a dose-dependent increase in the amplitude of the startle response ($P < 0.001$, Friedman, two-way ANOVA; Fig. 2). The increase was statistically significant at 0.2 and 0.8 mg/kg. No significant change in the startle latency was observed. At higher doses the animals showed a pronounced 5-HT syndrome and salivation.

Pergolide: Pergolide was found to have no significant effects on startle behaviour at the doses tested (0.2 and 0.8 mg/kg; Fig 3), besides prolongating the startle latency at 0.2 mg/kg ($P < 0.02$, Wilcoxon *t*-test). Closer observation of the animals revealed a slight increase in stereotyped sniffing behaviour. Doses above 0.8 mg/kg were lethal.

Bromocriptine: No significant effect was seen on startle amplitude after treatment with bromocriptine at 5 or 20 mg/kg (Fig. 3). However, the startle latency was dose-de-

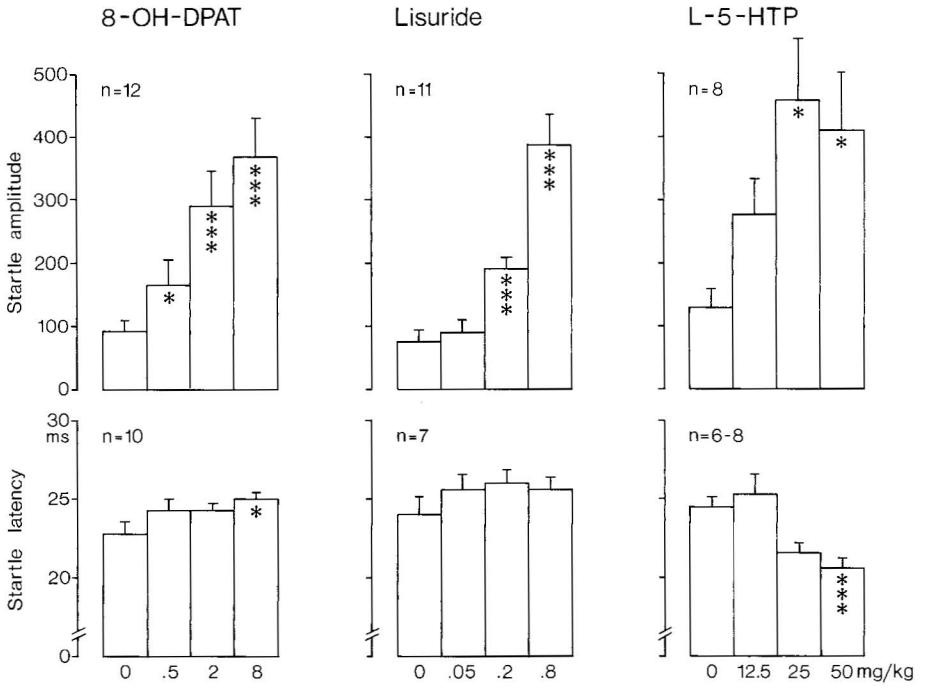

Fig. 2. Effects of 8-OH-DPAT, lisuride and 5-HTP on the acoustic startle response in the rat. Animals treated with 8-OH-DPAT and lisuride served as their own controls in a balanced design in two separate groups ($n = 12$), while 5-HTP-treated animals were tested only once in four separate groups ($n = 8$). The former durgs were given IP 10 min before startle measurements, 5-HTP IP 1 h before. 5-HTP treated animals and corresponding controls were pretreated with pargyline, 75 mg/kg IP 4 h before testing and beserazide, 25 mg/kg IP 1.5 h before testing. The averaged means over 20 trials ± SEM are shown in the figure. Statistical analysis was performed by means of Friedmann two-way ANOVA followed by Wilcoxon *t*-test (8-OH-DPAT and lisuride) and Kruskal-Wallis one-way ANOVA followed by Mann-Whitney *U*-test (5-HTP). *Startle amplitude* 8-OH-DPAT: $\chi^2_r(3) = 24.70$, $P < 0.001$; Lisuride: $\chi^2_r(3) = 23.72$, $P < 0.001$; 5-HTP: $\chi^2(3) = 7.76$, $P < 0.05$. *Startle latency* 8-OH-DPAT: $\chi^2_r(3) = 11.43$, $P < 0.01$; Lisuride: $\chi^2_r(3) = 3.51$, NS1 5-HTP: $\chi^2(3) = 12.31$, $P < 0.01$. $^*P < 0.05$; $^{***}P < 0.01$

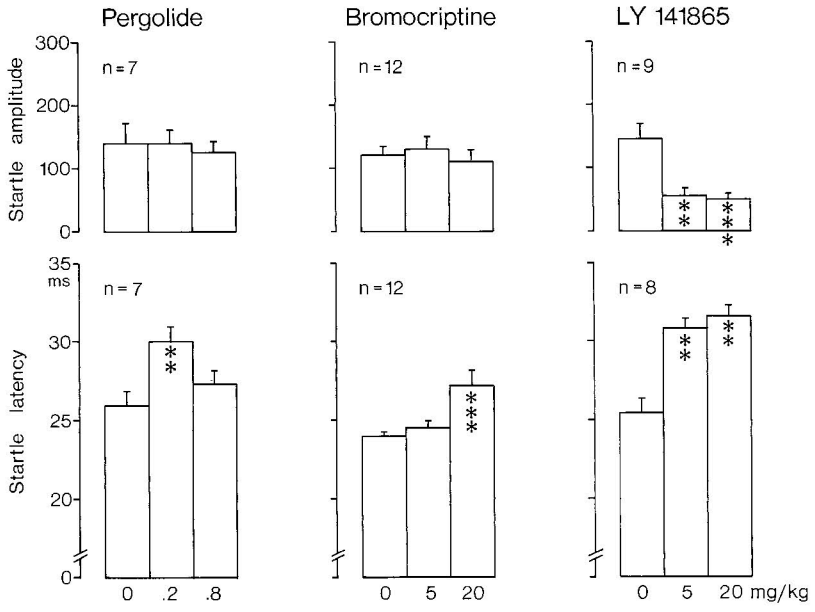

Fig. 3. Effects of pergolide, bromocriptine and LY141865 on the acoustic startle response in the rat. The animals served as their own controls in a balanced design in three separate groups ($n = 7$, $n = 12$, and $n = 12$ respectively). Pergolide was given SC 2 h before testing, bromocriptine SC 3 h before testing and LY 141865 IP 10 min before testing. Results are represented by the averaged means over 20 trials ± SEM in the figure. Statistical analysis was performed by means of Friedman two-way ANOVA followed by Wilcoxon *t*-test. *Startle amplitude* Pergolide: $\chi^2_r(2) = 1.14$, NS; Bromocriptine: $\chi^2_r(2) = 0.66$, NS; LY 141865: $\chi^2_r(2) = 6.22$, $P < 0.05$. *Startle latency* Pergolide: $\chi^2_r(2) = 8.35$, $P < 0.05$; Bromocriptine: $\chi^2_r(2) = 9.50$, $P < 0.01$; LY 141865: $\chi^2_r(2) = 6.75$, $P < 0.05$. $^*P < 0.05$; $^{***}P < 0.001$

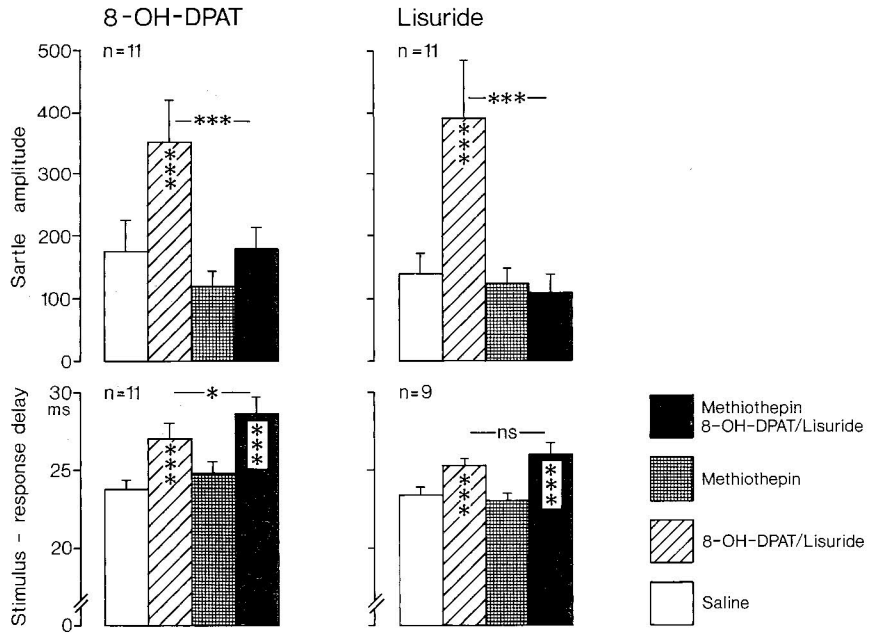

Fig. 4. Effects of methiothepin in combination with 8-OH-DPAT and lisuride on the acoustic startle response in the rat. The animals served as their own controls in a balanced design in two separate groups ($n = 12$). Methiothepin (0.1 mg/kg) was given IP 70 min before testing, 8-OH-DPAT (2 mg/kg)/lisuride (0.2 mg/kg) IP 10 min before. The averaged means over 20 trials ± SEM are shown in the figure. Statistical analysis was performed by means of Friedman two-way ANOVA followed by Wilcoxon *t*-test. *Startle amplitude* Methiothepin + 8-OH-DPAT: $\chi^2_r(3) = 14.67$, $P < 0.01$; Methiothepin + lisuride: $\chi^2_r(3) = 13.36$, $P < 0.01$. *Startle latency* Methiothepin + 8-OH-DPAT: $\chi^2_r(3) = 16.20$, $P < 0.01$; Methiothepin + lisuride: $\chi^2_r(3) = 17.66$, $P < 0.001$. $^*P < 0.05$; $^{***}P < 0.01$

pendently increased ($P < 0.01$, Friedman two-way ANOVA). The increase was statistically significant at 20 mg/kg.

LY 141865: LY 141865 caused a dose-dependent decrease in startle amplitude ($P < 0.05$, Friedman two-way ANOVA; Fig. 3). The decrease was statistically significant at both doses tested (5 and 20 mg/kg). The startle latency was increased ($P < 0.05$, Friedman two-way ANOVA) and significant at both doses. Informal observation revealed increased sniffing behaviour and spontaneous ejaculations were frequently seen at 20 mg/kg.

Effects of methiothepin and metergoline on the 8-OH-DPAT and lisuride induced stimulation of the startle response

Methiothepin: Methiothepin (0.1 mg/kg) significantly antagonized the stimulatory effect of both 8-OH-DPAT (2 mg/kg) and lisuride (0.2 mg/kg) on startle amplitude

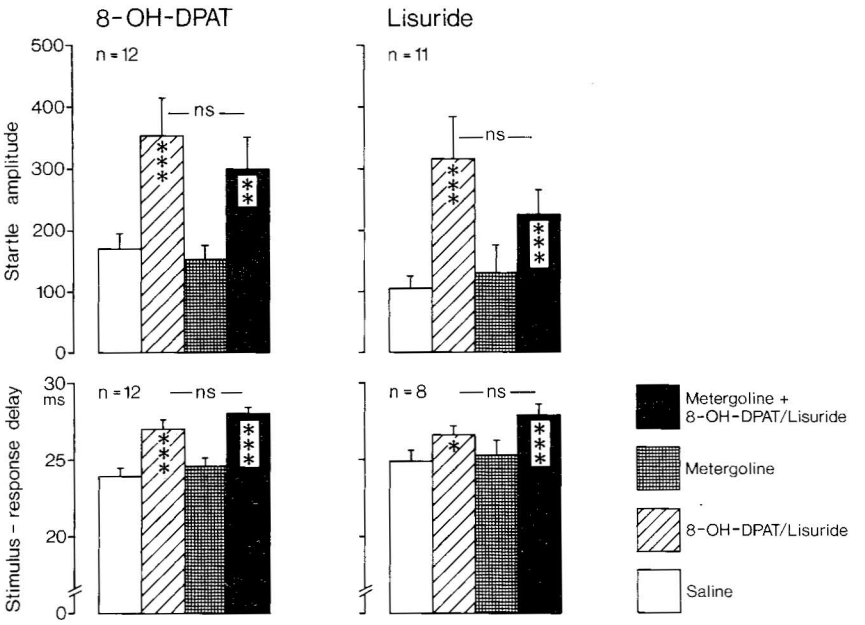

Fig. 5. Effects of metergoline in combination with 8-OH-DPAT and lisuride on the acoustic startle response in the rat. The animals served as their own controls in a balanced design in two separate groups ($n = 12$) Metergoline (1 mg/kg) was given IP 70 min before testing, 8-OH-DPAT (2 mg/kg)/lisuride (0.2 mg/kg) IP 10 min before. The averaged means over 20 trials ± SEM are shown in the figure. Statistical analysis was performed by means of Friedman two-way ANOVA followed by Wilcoxon *t*-test. *Startle amplitude* Metergoline + 8-OH-DPAT: $\chi^2_r(3) = 21.70$, $P < 0.001$; Metergoline + lisuride: $\chi^2_r(3) = 9.21$, $P < 0.05$. *Startle latency* Metergoline + 8-OH-DPAT: $\chi^2_r(3) = 17.82$, $P < 0.001$; Metergoline + lisuride: $\chi^2_r(3) = 10.54$, $P < 0.05$. $^*P < 0.05$; $^{**}P < 0.02$; $^{***}P < 0.01$

(Fig. 4). Methiothepin alone did not significantly alter the startle amplitude or the startle latency compared to saline treated controls. 8-OH-DPAT and lisuride alone increased the average amplitude of the startle response ($P < 0.01$, Wilcoxon *t*-test) while 8-OH-DPAT and lisuride in combination with methiothepin did not significantly differ from controls. Both 8-OH-DPAT and lisuride were found to significantly prolong the startle latency in this experiment ($P < 0.01$, Wilcoxon *t*-test). The prolongation was not counteracted by methiothepin, but in fact slightly increased for 8-OH-DPAT ($P < 0.05$, Wilcoxon *t*-test).

Metergoline: Metergoline (1 mg/kg) did not significantly antagonize the stimulatory effect of either 8-OH-DPAT (2 mg/kg) or lisuride (0.2 mg/kg) on startle amplitude (Fig. 5). 8-OH-DPAT and lisuride alone caused a statistically significant increase in the average startle amplitude and a prolongation of the startle latency compared to saline-injected controls ($P < 0.01$, Wilcoxon *t*-test). Neither of these effects were significantly counteracted by metergoline.

Discussion

The present findings show that 8-OH-DPAT and the ergot derivative lisuride, which is supposed to exert both 5-HT and DA-receptor agonist activity (Kehr 1977), have similar effects on the acoustic startle response in the rat. Both agents markedly increase the startle amplitude and prolong the startle latency (Fig. 2). The increase in startle amplitude is of approximately the same magnitude as the large increase in response seen after 5-HTP treatment in pargyline- and benserazide-pretreated animals (Fig. 2). Lisuride, however, seems to be roughly ten times as potent as 8-OH-DPAT, an interesting observation as it correlates well with the two drugs ability to reduce 5-HT synthesis rate (Hjorth et al. 1982). These observations suggest that the two compounds affect a common CNS mechanism.

The data concerning the antagonistic potential of methiothepin and metergoline on these effects clearly indicates methiothepin to be the more potent. Under the experimental conditions prevalent, methiothepin (0.1 mg/kg) completely negated the effect on startle amplitude caused by both 8-OH-DPAT (2 mg/kg) and lisuride (0.2 mg/kg) (Fig. 4), whereas metergoline (1 mg/kg) did not significantly alter any of the responses (Fig. 5). However, neither of the antagonists had any visible effect on the prolongation of the startle latency.

It is difficult to explain the discrepancy in the two antagonists' ability. However, a possible explanation might be derived from some recent binding studies concerning the 5-HT receptor affinity of 8-OH-DPAT. In the work of Middlemiss and Fozard (1983) it was concluded that 8-OH-DPAT binds rather selectively to a subpopulation of 5-HT receptors, the high-affinity 5-HT_{1A} receptor sites (Pedigo et al. 1981). Neither the low-affinity 5-HT_{1B} binding sites nor the 5-HT_2 binding sites were found to bind 8-OH-DPAT to any appreciable extent. Thus, 8-OH-DPAT may act on a subpopulation of 5-HT receptors, a property which it may share with lisuride. Further studies are necessary to see whether methiothepin has a similar affinity, but indeed binding studies concerning the possibility of methiothepin and metergoline being 5-HT autoreceptor antagonists show different pharmacological properties between the two antagonists (cf Göthert 1982). Moreover, in the study by Hjorth et al. (1982), methiothepin but not metergoline was able to antagonize the 8-OH-DPAT-induced 5-HT syndrome, a syndrome widely believed to reflect serotonin receptor activation (Jacobs 1976).

The functional importance of the selective activation of the spinal vs the supraspinal subpopulation of 5-HT receptors has been emphasized by Davis et al. (1980b). In that study it was shown that the local application of 5-HT to spinal 5-HT receptors increases startle, whereas intracerebroventricular administration decreased it. It is possible that 8-OH-DPAT and lisuride exert selective effects on the spinal subpopulation of 5-HT receptors, which may explain why these drugs increase startle. Further evicence for an interaction of 8-OH-DPAT with spinal 5-HT receptors is provided by the possibility of 5-HT_{1A} binding sites in the spinal cord (Monroe and Smith 1983).

In the interpretation of these data, however, it must be considered that methiothepin is not a pure 5-HT receptor antagonist, but possesses both DA and NA receptor antagonist properties as well (Lloyd and Bartholini 1974). Thus, it cannot be excluded that the DA receptor agonist activity exerted by lisuride (Horowski and Wachtel 1976; Kehr 1977) contributes to the effects on startle response. A direct interaction of 8-OH-DPAT with DA mechanisms is less likely, since this drug seems to lack DA-receptor activity (Hjorth et al. 1982).

It is interesting to note that pergolide, bromocriptine, and LY 141865, three mainly DA-receptor active ergot-related drugs (Fuller et al. 1979; Fuxe et al. 1975a; Tsuruta et al. 1981), all seem to be without stimulatory effect on the acoustic startle response (Fig. 3). LY 141865 in fact reduces the response. These drugs thereby fail to support the suggestion that an increased DA transmission increases startle response (Davis 1980).

The startle latency was measured as the time in milliseconds from the presentation of an acoustic stimulus to the animal to the registration of a response-elicited accelerometer voltage (Fig. 1). This method gave rise to a considerably longer response latency compared to those normally registered (cf Horlington 1968). This increase is by all means due to the particular use of the accelerometer. As can be seen in Fig. 1, the accelerometer was orientated for maximal positive voltage peak readings, with the consequence of an approximately 10-ms method-related lenghtening of the startle latency.

Despite the relative small differences in startle latencies between treatment groups, the differences within a single animal were very consistent. This is also indicated by the relatively small number of animals needed for significant results in the statistical analysis. Hence, this seldom used unit of startle activity measurement may provide a useful tool in the evaluation of startle behaviour.

Surprisingly, a prolongation of the startle latency was registered concomitant with the increase in startle amplitude caused by 8-OH-DPAT and lisuride (Fig. 2). The effect was present for both "high" and "low" responders. The question is further complicated by the fact that 5-HTP administered to pargyline and beserazide pretreated animals causes a significant shortening of the startle latency (Fig. 2). Needless to say, further investigations must be conducted to explain the nature of this effect.

A prolongation of the startle latency was also recorded for the three mainly DA-receptor active ergot derivatives (Fig. 3). A similar effect has also been registered for the well known DA-receptor agonist apomorphine (Svensson, in preparation). The effect of apomorphine is thereby the opposite to that of 5-HTP, indicating difference between the DA and 5-HT systems regarding this variable.

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