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Effects of Metergoline and Quipazine on Locomotor Activity of Rats in Novel and Familiar Environments

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BENINGER, R. J. *Effects of metergoline and quipazine on locomotor activity of rats in novel and familiar environments.* PHARMACOL BIOCHEM BEHAV **20**(5) 701–705, 1984.—Many studies have investigated the effects on locomotor activity of various manipulations of the brain's serotonin (5-hydroxytryptamine, 5-HT) systems but the results have not been consistent. However, besides employing different techniques for manipulating brain 5-HT, previous studies have differed in size of apparatus, amount of apparatus pre-exposure and length of session. To test the possibility that apparatus familiarity interacts with the effects of 5-HT manipulations on locomotor activity, this variable was manipulated in groups of rats treated with the 5-HT receptor blocker, metergoline or the agonist, quipazine. Within each drug treatment group, 18 rats had prior experience with the activity monitoring photocell chambers (pre-exposed condition) and 18 were not previously exposed (novel condition); each condition was further subdivided into 3 dose subgroups (n=6). Testing consisted of 3 30-min sessions with subgroups receiving metergoline (0, 2.5, 5.0 mg/kg) or quipazine (0, 2.5, 5.0 mg/kg) 30 min before. Results with metergoline treatment revealed no significant drug effect in the pre-exposed groups but a decrease in activity in the novel condition. Quipazine, on the other hand, had no significant effect in the novel condition but produced a time-dependent effect on activity in the pre-exposed condition. These results suggest that the effects on locomotor activity of compounds affecting 5-HT neurotransmission may interact with the familiarity of the test apparatus and with the duration of testing. Interexperiment differences in these variables may account for some of the inconsistencies previously reported.

Metergoline Quipazine Locomotor activity Serotonin

EXPERIMENTAL manipulations that alter transmission at serotonin (5-hydroxytryptamine, 5-HT) synapses in the brain often produce changes in locomotor activity [12]. Results have not been consistent, however. For example animals treated with the 5-HT synthesis inhibitor, parachlorophenylalanine (PCPA) have been reported to increase activity [7,25], show no significant change [35] and decrease locomotor activity [36]. Similarly, neurotoxic destruction of the nuclei of origin of the brain's ascending 5-HT systems with 5,6- or 5,7-dihydroxytryptamine (DHT) produces variable results [13, 14, 19, 21].

The effects of electrolytic lesions of the raphe nuclei have been more consistent, usually resulting in increased activity [33]. However, this treatment has been shown to produce different effects on locomotor activity in direct comparisons with 5,7-DHT lesions [19] and PCPA [18]; therefore, it has been suggested that the effects of electrolytic lesions might be the result of damage to nonserotonergic structures [20].

Gerson and Baldessarini [12] suggested that the effects of decreased forebrain 5-HT on activity may interact with the novelty of the test environment. Thus, animals treated with PCPA or DHT evidence no change or increased activity in familiar home cages but decreased activity in novel environments such as an open field [13, 21, 22]. These findings are consistent with the novelty hypothesis but other interpretations are possible since variables such as size of apparatus, illumination, background noise, treatment-test interval and duration of testing covaried with novelty in these studies.

The present experiment was undertaken to study the possible interactive effects on locomotor activity of apparatus familiarity and compounds known to influence 5-HT synaptic transmission. Familiarity was manipulated by preexposing some rats to the test environment prior to testing and pharmacological agents known to have specific influences on 5-HT receptors were used [8]. Thus, 5-HT synaptic transmission was reduced with the receptor blocker, metergoline [1, 10, 11] or increased with the direct acting agonist, quipazine [9, 15, 27]. Note that at the two doses employed here, quipazine has been reported to be without significant effect on dopamine metabolites in the striatum [26,28]; however, the results of some drug discrimination studies suggest the possibility that even low doses of quipazine may have a dopaminergic action [29].

METHOD

Subjects

Seventy-two experimentally naive male Wistar albino rats weighing 200–250 g were individually housed in a climatically controlled colony room kept on a 12 hr light (6:00–18:00 hr)/dark cycle. Food and water always were available in the home cage.

Apparatus

Activity was monitored in six similar Plexiglas-R chambers (41×50.5×37 cm) each housed in a styrofoam-insulated wooden sound-attenuating box illuminated by an overhead bulb (2.5 watt) and ventilated by a small fan that also provided constant masking noise. Each chamber was outfitted with 7 infrared emitters and detectors, 4 being spaced at 10 cm intervals along the length of the chamber and 3 along the width, all at a height of 5 cm above the grid floor. Locomotor activity was monitored independently in each chamber with the use of a single board microcomputer (Cromemco) with its user interface being a printing terminal.

Procedure

All rats were handled for 5 min per day for 5 days prior to the initiation of pre-exposure sessions. Thirty-six rats then received 5 30-min sessions of pre-exposure to the test chambers; sessions occurred at approximately the same time each day and each rat always was tested in the same chamber. To control for handling on each of these 5 days, rats in the non-pre-exposure condition were placed for 2 5-min periods into the transporting boxes used for the pre-exposure groups.

Testing occurred on the following 3 days. Eighteen of the pre-exposed rats and 18 rats for which the test chambers were novel constituted the metergoline groups, the remaining 18 pre-exposed and 18 non-pre-exposed rats making up the quipazine groups. The 18 rats within each familiarity condition were further subdivided into 3 groups (n=6). Three doses of each drug were employed, each dose being given to one subgroup within each familiarity condition.

Metergoline (Farmitalia) was suspended in a small quantity of the polymer, polyoxyethylene sorbitan mono-oleate (Tween 80) added to distilled water to an appropriate concentration to yield a constant injection volume of 2 ml/kg body weight. Doses of 0 (Tween in water), 2.5 and 5.0 mg/kg were injected IP 30 min prior to testing. Quipazine maleate (Polysciences) was dissolved in distilled water and always was injected in a volume of 1.0 ml/kg. Doses of 0 (saline), 2.5 and 5.0 mg/kg were injected IP 30 min prior to testing.

Total activity was recorded for each 10 min segment of the 30-min test sessions. After 3 sessions, inspection of the data for the pre-exposed quipazine groups revealed a possible interaction between the drug effect and time. To further assess this possibility, one additional lengthened (40 min) test session was conducted on the following day for the 6 quipazine subgroups.

RESULTS

The effects of each drug on activity counts in each familiarity condition were considered separately. Thus, 4 analyses of variance (ANOVAs) were conducted, one for each of the metergoline novel, metergoline pre-exposed, quipazine novel and quipazine pre-exposed conditions. In each case, a 3-variable ANOVA with repeated measures on 2 variables was carried out; the variables analysed were time, session and drug dose, the former 2 being repeated measures. It should be noted that activity counts decreased significantly over the 5 pre-exposure days for all pre-exposed groups. As a result, the level of activity in vehicle-treated rats in each novel condition was higher than that of the corresponding pre-exposed group. There also was a consistent within-session decrease in activity in the vehicle groups.

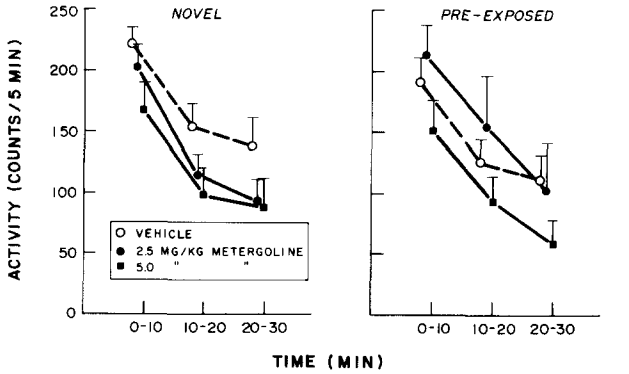

FIG. 1. Mean (±S.E.M.) locomotor activity (counts/5 min) averaged over 10 min segments of 3 test sessions for groups receiving metergoline and tested in novel (left) and familiar (right) chambers. Both conditions showed significant effects of time but the drug dose was significant only for the novel condition.

In order to keep these between group differences and within session changes clear to the reader, drug data were not converted to a percent of vehicle although such a change would make the drug effects clearer to see. Each range of drug doses within a novel or pre-exposed group was considered separately with respect to the relevant vehicle group.

Results for the metergoline novel condition revealed a significant main effect of time ($p<0.001$), session ($p<0.05$) and drug dose ($p<0.01$). As none of the interactions were significant, data were collapsed over the 3 test sessions and the group mean (±S.E.M.) activity levels (counts per 5 min) are shown in Fig. 1. The time effect is indicated as a decrease in activity for all groups over the course of the session.

Analysis of the metergoline pre-exposed condition yielded main effects of time ($p<0.001$) and session ($p<0.02$); the drug effect was not significant ($0.05<p<0.1$), nor were the interactions. From Fig. 1 it appears that the low dose (2.5 mg/kg) may have produced a slight increase in activity whereas the higher dose produced a decrease relative to vehicle; however, these effects were not significant.

Mean activity counts for the quipazine novel groups, collapsed over the first 3 test sessions are shown in Fig. 2. (The extra test session was treated separately; see below.) Analysis of variance of these data yielded only a main effect of time ($p<0.001$); all other main effects and interactions were not significant.

The quipazine pre-exposed groups, on the other hand, revealed not only a time effect ($p<0.001$) but also a sessions effect ($p<0.005$) and a significant time × drug dose interaction ($p<0.02$). Inspection of the right panel of Fig. 2 suggests that this interaction occurred because, whereas the pre-exposed vehicle group showed a large decline in activity over time, the pre-exposed drugged animals showed a much smaller time effect, initially being less active than vehicles but showing a trend towards greater activity than vehicles in the 20 to 30 min time segment.

The extra lengthened test session for the quipazine groups was conducted to further assess the possibility that the drugged animals in the pre-exposed condition would actually be more active than vehicles late in the session. The results (Fig. 3) confirmed the previous findings. Thus, the quipazine novel groups showed only a time effect ($p<0.001$) whereas the quipazine pre-exposed groups again showed not only a

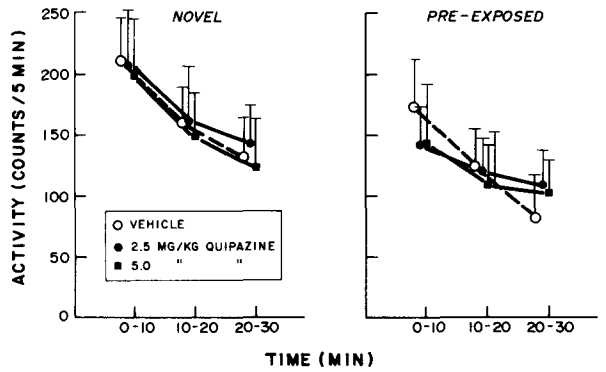

FIG. 2. Mean (±S.E.M.) locomotor activity (counts/5 min) averaged over 10 min segments of 3 test sessions for groups receiving quipazine and tested in novel (left) and familiar (right) chambers. Both conditions showed significant effects of time but the drug × time interaction was significant only for the pre-exposed condition.

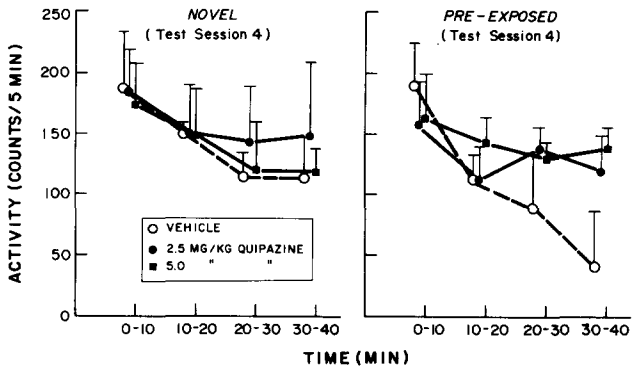

FIG. 3. Mean (±S.E.M.) locomotor activity (counts/5 min) for 10 min segments of the extra, lengthened test session for the quipazine groups tested in a novel (left) or familiar (right) environment. Both conditions showed significant effects of time but the drug dose and drug × time interaction was significant only for the pre-exposed condition.

time effect ($p<0.001$) but also a dose effect ($p<0.02$) and a time × drug dose interaction ($p<0.002$). This interaction was confirmed by post hoc one way ANOVAs of the time effect within each dose group; the time effect was significant for the vehicle group ($p<0.001$) but not for the 2 drug groups. Of particular note, the 2.5 and 5.0 mg/kg quipazine pre-exposed groups showed minimal effects of the drug in the first 20 min but greater activity than control in the final 20 min.

DISCUSSION

The results revealed that the 2 doses of metergoline produced a significant decrease in locomotor activity in a novel but not in a familiar test environment. Note that the locomotor effects of metergoline in the pre-exposed group were marginally significant ($p<0.10$); thus, the higher dose reduced activity somewhat. However, the low dose, while significantly reducing activity in the novel condition produced an insignificant increase in activity in the pre-exposed group. Quipazine, on the other hand, while having no significant effect on activity in a novel environment produced a time dependent increase in animals familiar with the test chamber; this increase was observed in the latter portion of the session. It is noteworthy that at dose levels up to 5.0 mg/kg, quipazine has been found to be without significant effect on dopamine metabolites [26,28] suggesting that the observed effects may have been mediated by changes in serotoninergic neurotransmission; however, this conclusion must be viewed with caution as the results of drug discrimination studies indicate a possible dopaminergic influence of quipazine [29].

The effects of metergoline in the novel condition are consistent with the results of studies that employed novel test environments and reported data for 30 min or less when testing the effects on locomotor activity of manipulations that reduce brain 5-HT. Thus, locomotor activity was decreased following PCPA [22,36], parachloroamphetamine (PCA [37]) and 5,6-DHT or 5,7-DHT lesions [6, 13, 21].

Contrary to these findings, some studies have reported that PCPA [7, 18, 25, 35] or 5,7-DHT [5,19] were without significant effect on locomotor activity during the first 30 min or less in a novel environment. However, 5 of these 6 studies used small environments (floor space <4,000 cm^2) whereas 5 of the 7 studies reporting significant decreases in activity used large test environments (>5,000 cm^2). Since animals are typically housed in small cages, size of test apparatus may contribute to relative novelty. Perhaps, animals with reduced 5-HT function show decreased locomotor activity in a novel environment when it is large but less often when it is small.

In some studies rats were pre-exposed to the environment prior to testing the effects of decreasing 5-HT on activity for up to 30 min. Consistent with the present observation of no significant effect of metergoline in this situation, others have found PCPA [35,36] and 5,7-DHT lesions [14] to be without significant effect.

There have been fewer studies of the effects of enhanced 5-HT neurotransmission on locomotor activity tested for 30 min or less. It has been found that treatment with the substrate amino acid for 5-HT, tryptophan or the 5-HT precursor, 5-hydroxytryptophan (5-HTP) reduced activity in a novel environment [24,34]. However, 5-HTP plus a peripheral decarboxylase inhibitor resulted in enhanced activity [24] raising the possibility that some of the activity-depressing effects of tryptophan or 5-HTP alone may be due to peripheral influences (cf., [16]). In the present study, quipazine was without significant effect on activity in a novel test chamber; since quipazine is known to act centrally [9] the reconciliation of this finding with previous results awaits further study.

Mention should be made of the effects of 5-HT manipulations on activity assessed for a period of greater than 60 min. In this situation, activity is significantly *increased* by PCPA [4, 7, 21, 22, 25], PCA [23] and 5,7-DHT lesions of the raphe nuclei [21]. One exception is the report of decreased running wheel activity 4 weeks after 5,7-DHT lesions [31]. Conversely, activity measured over long test sessions is reduced by systemic injections of the 5-HT precursor, 5-HTP [16,17], 5-HT itself [16], or by intracerebroventricular 5-HT [38]. The contribution of peripheral influences to the effects of systemic 5-HTP on activity requires consideration as injection of 5-HTP plus a peripheral decarboxylase inhibitor results in increased activity during a 90 min test session [30]. Thus when long test sessions are employed, manipulations that decrease 5-HT neurotransmission usually increase activity and conversely, those that increase 5-HT attenuate activity.

In conclusion, serotonin appears to play an important role in modulating the level of general locomotor activity of animals. When short test sessions (30 min or less) are employed and the apparatus is novel, reduced 5-HT function usually leads to decreased activity; this was shown in the present study with metergoline and by others with PCPA, PCA, 5,6- and 5,7-DHT. In this situation, increased 5-HT neurotransmission following treatment with the direct acting agonist, quipazine is without significant effect whereas the central effects of the 5-HT precursors, tryptophan or 5-HTP remain equivocal. With short test sessions in a familiar apparatus, metergoline or other treatments that reduce 5-HT neurotransmission are usually without significant effect whereas quipazine produces little effect early in the session but may actually result in increased locomotor activity late in the short test session. These results suggest that the locomotor effects of drugs reported to influence serotonergic neurotransmission may interact both with the familiarity of the test environment and with the duration of the test session.

It is possible that the influence of apparatus familiarity on the short-term locomotor effects of manipulations of serotonergic systems is related to previous data suggesting a role for serotonin in certain forms of learning. Thus, it has been found that serotonin may play a role in "tuning out" or learning to ignore non-reinforced or irrelevant stimuli; this hypothesis was suggested by the findings that habituation was slowed [4], latent inhibition was blocked [32] and responding in extinction was increased by PCPA [2]. Perhaps this putative serotonergic "tuning out" process normally is engaged when an animal encounters novel stimuli, for example in a novel activity monitor. Treatments that reduce serotonergic neurotransmission may lead to decreased activity because of enhance freezing elicited by unattenuated novel stimuli; treatments that increase serotonin in novel environments may have little effect because serotonin functioning already is high according to this scheme. In familiar environments, serotonin blockers may have little effect since the behavioural influence of environmental stimuli already has been reduced; in this situation, serotonin agonists might be expected also to have little effect. The observed increase in locomotor activity of quipazine-treated rats tested in a familiar environment, therefore, remains to be explained. If this compound influences dopaminergic neurotransmission, as some data suggest [29], it may be this effect that results in the quipazine-produced activity increase.

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