Pharmacology Biochemistry & Behavior, Vol. 22, pp. 885–887, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

BRIEF COMMUNICATION

Effects of Quipazine and Methysergide on Play in Juvenile Rats

LARRY NORMANSELL AND JAAK PANKSEPP

Department of Psychology, Bowling Green State University, Bowling Green, OH 43403

Received 27 January 1984

NORMANSELL, L. AND J. PANKSEPP. *Effects of quipazine and methysergide on play in juvenile rats.* PHARMACOL BIOCHEM BEHAV 22(5) 885–887, 1985.—Social play of juvenile rats was analyzed following administration of either the serotonin receptor agonist quipazine (1, 2.5, 5 and 10 mg/kg) or the antagonist methysergide at the same doses. Quipazine reduced pinning at all doses, while methysergide did so at only the highest two. An interaction study using the lowest doses of the agents used above, indicated that methysergide could reverse quipazine induced reductions of play. Thus, the quipazine effect was probably mediated through a serotonin receptor; however, the role of serotonin in play appears to be a general modulatory one rather than a specific influence on play.

Play Quipazine Methysergide Serotonin Rats

PLAY in juvenile rats is a vigorous social behavior characterized by flurries of complex motor sequences including intense social grooming, chasing, leaping, pouncing, wrestling, and occasionally mounting and boxing. A common and distinct component of the wrestling sequences, the pin—one animal on its back with the other on top—is an easily quantified, objective measure which correlates highly with more subjective measures of rough-and-tumble play activities [8,9]. Using this as an indicator variable, pharmacological manipulations which may increase or decrease play can be conveniently studied [8,10].

Many psychopharmacological agents affect play [15]. Catecholamine agonists [3] and antagonists [2,8] reduce play. As is apparent in the previous study of this series, clonidine, an α-2-adrenergic agonist, reduces play, but yohimbine, a drug which can block that receptor, has no effect [7]. Presumably, for a brain neurochemical system to be specifically involved in a behavior, opposite fluctuations of activity at relevant synapses (for instance, via administration of receptor agonists and antagonists) should lead to opposing behavioral changes. The only system for which this has presently been demonstrated is brain opioids. Morphine, a mu receptor agonist increases play [8,12] while naloxone, a mu receptor antagonist, reduces play [1,8].

In the present experiment we investigated the effects of manipulating the serotonergic system on subsequent play in juvenile rats using the direct acting agonist quipazine [4], and an antagonist, methysergide [5]. Although it is uncertain whether these substances affect periadolescent animals differently than they do adults, there do not appear to be age-related behavioral discontinuities in the action of another serotonergic agonist, fenfluramine (Spear and Ristine, unpublished observation; cited in [14]). A dose response relationship for each drug was first established and neurochemical specificity was then tested by interacting the two drugs.

METHOD

Subjects

Fifty-two male and female Long-Evans hooded rats from 6 litters bred and born at BGSU were used. Animals were housed in family groups in suspended solid bottom cages (24×40×19 cm) with woodchip bedding until they were weaned at 21 days of age. Subjects were then assigned a like-sex partner for subsequent play tests and rehoused individually in wire bottom cages (23×10×13 cm). The colony room was maintained on a 12:12 hr light:dark cycle (lights on at 0800) and food and water was continuously available.

Apparatus

The play testing chamber has been described before [11]. Briefly, it was a Lucite test arena (31×31×32 cm) situated within a soundproof outer chamber with a 10×10 cm observation window. An observer scored the play behavior of each animal during a 5 min test session. The primary dependent measure, a pin, occurred whenever one animal ended up on its back during the course of rough and tumble play activity. Interobserver reliability for such observations are routinely above 0.9 in our laboratory. In the present study, the frequency and duration of pins were recorded with a manually activated counter and running time meter. All testing occurred during the second half of the light cycle.

TABLE 1

EFFECTS OF QUIPAZINE ON PINNING (MEANS ± SEM) AT EACH OF THE DESIGNATED DOSES

Quipazine Dose (mg/kg)	Pins/Pair/5 min	% of Control
Low Dose Response		
0	48.8 ± 8.2	
1.0	25.3 ± 3.2*	52%
2.5	21.7 ± 2.6*	44%
High Dose Response		
0	59.8 ± 6.9	
5.0	1.8 ± 0.7*	3%
10.0	0*	0%

Newman-Keuls comparisons: *$p<0.01$.

TABLE 2

EFFECTS OF METHYSERGIDE ON PINNING (MEANS ± SEM) AT EACH OF THE DESIGNATED DOSES

Methysergide Dose (mg/kg)	Pins/Pair/5 min	% of Control
Low Dose Response		
0	42.5 ± 4.6	
1.0	37.0 ± 3.2	87%
2.5	33.4 ± 4.0	79%
High Dose Response		
0	59.4 ± 3.4	
5.0	39.5 ± 3.2*	66%
10.0	35.6 ± 4.3*	60%

Newman-Keuls comparisons: *$p<0.01$.

RESULTS

Quipazine Dose Response

Beginning on the day following weaning, pairs of animals were allowed 2 days (5 min periods) of habituation to the test chamber. Twelve pairs of animals were randomly divided into 2 groups (low and high dose). Quipazine was administered subcutaneously in the nape of the neck in doses of 1.0 and 2.5 mg/kg (low dose) and 5.0 and 10.0 mg/kg (high dose), twenty minutes before testing. Animals in both high and low groups were tested for 3 consecutive days and received the 2 drug conditions and the saline control (1 ml/kg, in this as well as subsequent experiments) in a counterbalanced fashion. Statistical analysis in this and the subsequent experiments was performed using one-way ANOVA for repeated measures. Post hoc comparisons utilized a Newman-Keuls procedure.

All doses of quipazine tested, reliably reduced play (Table 1). In the low dose group, both the 1.0 and 2.5 mg/kg treatments differed from vehicle tests but not from each other. At neither of these doses were there any apparent signs of neurotoxicity. Likewise, in the high dose group, both 5 and 10 mg/kg reduced play to an even greater extent, but, again, they did not differ from each other. At both high doses, however, neurotoxicity typically associated with serotonin overactivity (shaking) was apparent. Average pin durations did not reliably differ across treatment conditions, and ranged from 1.6–2.8 seconds. No sex differences were observed.

Methysergide Dose Response

At the conclusion of the quipazine testing, the same twelve pairs of animals became subjects in the methysergide experiment. For three consecutive days each pair of animals was administered each of the following drug conditions in counterbalanced manner: 1.0 and 2.5 mg/kg methysergide maleate or saline control. On the next 3 days (age range: 33–35 days), all animals were tested under 3 additional counterbalanced conditions: 5 mg/kg and 10 mg/kg methysergide, and saline control.

Table 2 shows the mean number of pins at each of the methysergide doses and their corresponding percent changes from saline control. Neither 1.0 nor 2.5 mg/kg treated animals were reliably lower than controls. Both 5 and 10 mg/kg methysergide reduced play, although they did not differ from each other. Animals were in no apparent way motorically affected by the drugs.

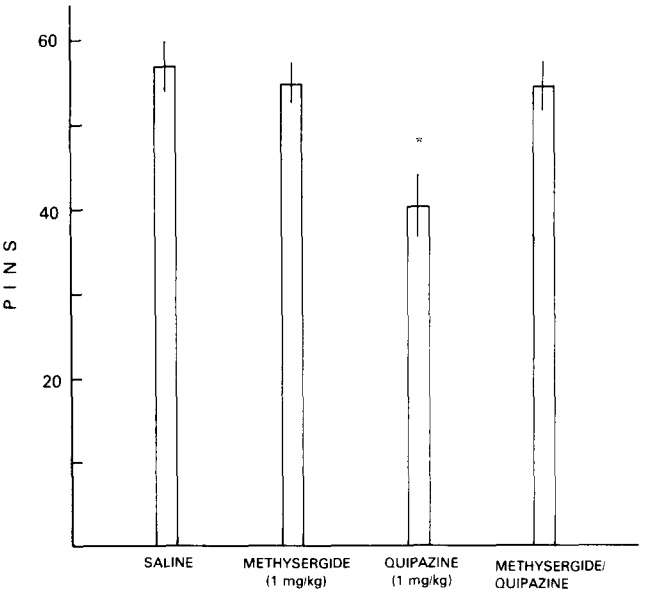

FIG. 1. Effect of quipazine-methysergide interaction on pinning behavior of juvenile rats. Each bar depicts mean number of pins (±SEM) per pair of animals in a 5 min observation period. Overall analysis, $F(3,39)=12.33$, $p<0.01$. Neuman-Keuls comparison, *$p<0.05$.

Quipazine-Methysergide Interaction

A drug interaction study was conducted using the lowest doses of drug employed in the previous dose-response studies. Fourteen drug naive pairs of animals were habituated to the testing chamber, and tested for four consecutive days 20 min following subcutaneous injections of 1 mg/kg quipazine, 1 mg/kg methysergide, 1 mg/kg quipazine combined with 1 mg/kg methysergide or 1 cc/kg of saline vehicle (age range: 24–27 days). Order of conditions was

counterbalanced and all animals were administered all conditions.

As in the previous experiments, quipazine reliably reduced play with no evidence of behavioral impairment, while methysergide had no effect (Fig. 1). Methysergide was, however, capable of completely antagonizing the quipazine-induced suppression. Average pin durations did not differ across groups, ranging from 1.7–1.9 sec.

DISCUSSION

Activation of serotonergic receptors with quipazine decreased the play of juvenile rats in a dose dependent manner. Although the two highest doses used also yielded moderate signs of neurotoxicity, following the low doses which also reduced play, animals appeared normal. The reduction of play following quipazine is expected not only from the fact that fenfluramine, a serotonin releasing agent powerfully decreases play [8], but also from the fact that activity of serotonin systems has long been related to behavioral arousal [6]. Facilitation of serotonin activity generally sedates animals while reductions in serotonin can lead to heightened arousal. A decrease in overall arousal should lower the tendency of animals to engage in active pursuits like play. At the same time it should be emphasized that general increases of arousal per se do not increase play. For instance, amphetamine reduces play, even at very low drug doses [2,3].

In the present experiment, blockade of serotonin systems with methysergide yielded no increase in the frequency of pinning, although a modest increase in a more subjective measure of play vigor (number of rough-and-tumble play bouts) was observed in our original work [8]. Additionally, the failure to detect an increase in play was probably not the result of a ceiling effect. We have tested other animals under lower baseline conditions (i.e., animals were group housed so the level of play during test sessions was uniformly low) and have also not detected any increase in play following methysergide treatment (Panksepp and Cox, unpublished data). To further evaluate whether we can increase play by reducing serotonin activity we have tested animals following inhibition of tryptophan hydroxylase with para-chlorophenylalanine and also animals sustained on tryptophan-free diets. Following both manipulations, animals exhibited powerful reductions in play, but those data are not presented because we do not believe they are capable of being clearly interpreted. Following both manipulations, animals appeared to be ailing, and it is not a surprise that sick animals will play less than normal. This, of course, is a problem for all manipulations that decrease play [13], and at the very least a neurochemically meaningful effect of a receptor agonist should be able to be countered by an appropriate antagonist. Thus, while methysergide administered alone did not increase play at low doses which are known to produce a substantial serotonin receptor blockade, it could reverse the play reduction induced by a low dose of quipazine. Although this indicates that quipazine reduced play via serotonin receptors, the absence of a reciprocal effect of agonists and antagonist, suggests that serotonin modulates play by some general influences on overall brain activity (e.g., sedation) as opposed to specific effects on play circuitry.

Since social play of juvenile rats is surely controlled by and expressed via a symphony of sensory, emotional and motor systems, no one neurochemical substrate should monopolize the diverse neuroanatomical infrastructure. While certain systems may play a direct lead in the moment to moment orchestration of the behavior (perhaps opioids constitute such a system [9]), others, such as serotonin, act in a more global regulatory manner, providing background management, not only for play but probably all other behaviors that mammals exhibit.

REFERENCES

1. Beatty, W. W. and K. B. Costello. Naloxone and play fighting in juvenile rats. *Pharmacol Biochem Behav* **17**: 905–908, 1982.
2. Beatty, W. W., K. B. Costello and S. L. Berry. Suppression of play fighting by amphetamine: Effects of catecholamine antagonists, agonists and synthesis inhibitors. *Pharmacol Biochem Behav* **20**: 747–755, 1984.
3. Beatty, W. W., A. M. Dodge, L. J. Dodge, K. White and J. Panksepp. Psychomotor stimulants, social deprivation and play in juvenile rats. *Pharmacol Biochem Behav* **16**: 417–422, 1982.
4. Hong, E., L. F. Sancilio, R. Vargas and E. G. Pardo. Similarities between the pharmacological actions of quipazine and serotonin. *Eur J Pharmacol* **6**: 274–280, 1969.
5. Jacoby, J. H., J. J. Poulakos and G. F. Bryce. On the central anti-serotonergic actions of cyproheptadine and methysergide. *Neuropharmacology* **17**: 299–306, 1978.
6. Jouvet, M. The role of monoamines and acetylcholine-containing neurons in the regulation of sleep-waking cycle. *Ergeb Physiol* **64**: 166–307, 1972.
7. Normansell, L. and J. Panksepp. Effects of clonidine and yohimbine on the social play of juvenile rats. *Pharmacol Biochem Behav* **22**: 881–883, 1985.
8. Panksepp, J. The regulation of play: neurochemical controls. *Soc Neurosci Abstr* **5**: 172, 1979.
9. Panksepp, J. Brain opioids—A neurochemical substrate for narcotic and social dependence. In: *Theory in Psychopharmacology*, vol 1, edited by S. Cooper. London: Academic Press, 1981.
10. Panksepp, J. The ontogeny of play in rats. *Dev Psychobiol* **14**: 327–332, 1981.
11. Panksepp, J. and W. W. Beatty. Social deprivation and play in rats. *Behav Neural Biol* **30**: 197–206, 1980.
12. Panksepp, J., J. Jalowiec, F. G. DeEskinazi and P. Bishop. Opiates and play dominance in juvenile rats. *Behav Neurosci*, in press, 1985.
13. Panksepp, J., S. Siviy and L. Normansell. The psychobiology of play: Theoretical and methodological perspectives. *Neurosci Biobehav Rev* **8**: 465–492, 1984.
14. Spear, L. P. and S. C. Brake. Periadolescence: Age dependent behavior and psychopharmacological responsivity in rats. *Dev Psychobiol* **16**: 83–109, 1983.
15. Thor, D. H. and W. R. Holloway, Jr. Social play in juvenile rats: A decade of methodological and experimental research. *Neurosci Biobehav Rev* **8**: 455–464, 1984.