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Dopamine Autoreceptor Agonists Attenuate Spontaneous Motor Activity But Not Spontaneous Fighting in Individually-Housed Mice

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WILMOT, C. A., T. A. FICO, C. VANDERWENDE AND M. T. SPOERLEIN. *Dopamine autoreceptor agonists attenuate spontaneous motor activity but not spontaneous fighting in individually-housed mice.* PHARMACOL BIOCHEM BEHAV 33(2) 387–391, 1989.—The present study was conducted to determine whether or not two behavioral characteristics of individually-housed mice, hyperactivity in a novel environment and intermale fighting, are attenuated by the dopamine (DA) agonists, apomorphine, (+)- and (−)-3-(3-hydroxyphenyl)-N-n-propylpiperidine (3-PPP). Autoreceptor-activating doses of these drugs which reduced spontaneous activity in a novel environment did not inhibit spontaneous fighting with conspecific olfactory bulbectomized males. Individually-housed mice were more active in a novel environment and showed a significant reduction of activity at lower doses of apomorphine, (+)- and (−)-3-PPP than group-housed mice. However, the ED_{50}'s for the inhibition of spontaneous activity in a novel environment in group- and individually-housed mice were similar: apomorphine, 0.02 vs. 0.012 mg/kg, SC; (+)-3-PPP, 0.50 vs. 0.51 mg/kg, SC; and (−)-3-PPP, 1.0 vs. 0.56 mg/kg, SC, for group- and individually-housed mice respectively. A significant proportion of individually-housed mice, but not group-housed mice, displayed catalepsy in response to high doses of (−)-3-PPP. These data suggest that DA autoreceptor agonists can modulate the hyperactivity syndrome but not spontaneous fighting behavior in individually-housed mice.

Differential housing Motor activity Isolation-induced fighting Dopamine autoreceptors Apomorphine 3-PPP

DIFFERENTIAL housing of male mice, i.e., housed singly or in groups, produces differences in the behavioral responses to a novel environment and to dopamine (DA) agonists (4, 24, 32, 36–38). Upon exposure to a novel environment or participation in fighting, the turnover of brain DA, norepinephrine (NE) and serotonin (5-HT) is significantly greater in individually-housed (IH) mice and rats compared to those group-housed (GH) (11, 15, 21, 22, 31, 33). Footshock stress also produces a greater acceleration of mesocortical DA turnover in IH rats compared to GH rats (3). In addition to changes in presynaptic neuronal activity in IH mice, there is behavioral evidence for an increased postsynaptic DA receptor sensitivity, although changes in the number or affinity of DA (D_2) receptors are not detectable (38). Whether or not there is a causal relationship between the increased sensitivity of dopaminergic systems, hyperactivity in a novel environment and fighting is not known.

Low doses of DA agonists inhibit spontaneous and amphetamine-induced motor activity and decrease the rate of DA synthesis and DA cell firing via a postulated interaction with DA autoreceptors (2, 6, 8, 9, 12, 13, 18, 19, 40). The objectives of the present study were 1) to determine if low doses of the DA agonists, apomorphine, (+)- and (−)-3-(3-hydroxyphenyl)-N-n-propylpiperidine (3-PPP) would inhibit spontaneous fighting in IH mice and 2) to compare the potency of these compounds for inhibiting spontaneous activity in both GH and IH mice. Higher doses of (−)-3-PPP produce behavioral and biochemical effects resembling DA antagonists but have not been shown to produce catalepsy (1, 13, 23, 25). Initial observations of IH mice treated with high doses of (−)-3-PPP noted catalepsy which was not observed in GH mice. A subsequent experiment was conducted to compare the response of IH and GH mice to high doses of (−)-3-PPP.

METHOD

Differential Housing

CF-1 male mice were obtained from Charles River Breeding

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Laboratory, Wilmington, MA, at 28 days of age and housed in groups of 15. At 34–38 days of age, the mice were either individually housed in a separate isolation room in cages measuring 28 × 12.5 × 14 cm or maintained grouped (15 per cage) in the colony room in cages measuring 45 × 27 × 14 cm. Food and water were continuously available. Housing conditions were maintained at 23 ± 2°C, 30–60% humidity and a 12-hr light-dark cycle with lights on at 6 a.m. After 4–5 weeks of differential housing, all behavioral testing occurred in the isolation room. Within their home cage, the group-housed mice were adapted to the isolation room for a minimum of 1 hour.

Fighting Test

IH mice were observed for fighting with an age-matched conspecific olfactory-bulbectomized male (stimulus mouse) as previously described (39), following the protocol of Gandelman *et al.* (10,35). Mice were tested 7 minutes following treatment with apomorphine, SC, or 15 minutes following (+)- or (−)-3-PPP, SC. These pretreatment times were selected so that the time interval for the fighting test coincided with the time of the maximal effects for reducing motor activity. Following the placement of the stimulus mouse in the home cage of the test mouse, the latency in seconds to the first fight and the total time spent fighting in seconds were recorded. The mice were observed for 5 minutes following the first fight or, if no fight occurred, for a total of 15 minutes. The first fight was defined by a bout of persistent biting with a minimum duration of 5 seconds. Fighting was initiated and terminated by the test mouse only. Each test mouse was subjected to only one fighting test. Stimulus mice were used repeatedly, provided their gross physical appearance and behavior appeared normal following a minimum of 1 day for recovery. Olfactory-bulbectomized stimulus mice have been shown to elicit fighting reliably with single or repeated use, but do not initiate a fight or retaliate (7). Fighting tests were conducted between 10 a.m. and 3 p.m.

Motor Activity

The effects of the test compounds on motor activity were assessed in separate groups of mice from those used in the fighting tests. Mice were placed individually into the center of a circular glass jar (8″ diameter) on electromagnetic activity meters (Columbus Instruments, Model S, calibrated to give equal sensitivity). Counts were recorded from 5 to 20 minutes after apomorphine or for 5 to 35 minutes after (−)- or (+)-3-PPP. Different time intervals for recording activity counts after apomorphine or 3-PPP were selected since low doses of apomorphine had a shorter duration of action for reducing spontaneous motor activity than (+)- or (−)-3-PPP. Mice from both housing conditions were tested on the same days, between 9 a.m. and 5 p.m., with dose and housing condition randomized over time. For the determination of ED_{50} for reducing motor activity, quantal data were obtained by calculating the percentage of mice in each dosage group which had cumulative activity counts less than one-half the mean activity counts for the respective group- or individually-housed control (vehicle) group. Thus, the ED_{50} for the reduction of motor activity represents that dose which reduces motor activity to one-half the activity counts of control groups in 50% of the mice tested.

Catalepsy

Mice were differentially housed for 4–5 weeks. Testing for catalepsy commenced 5 minutes after treatment with (−)-3-PPP and was repeated every 5 minutes for 30 minutes for a total of six

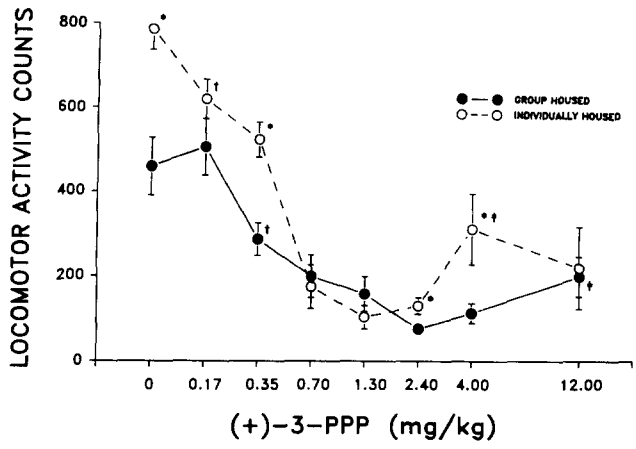

FIG. 1. Motor activity responses of differentially-housed mice to (+)-3-PPP. Mice were either group- or individually-housed for 4–5 weeks. Activity counts were recorded for 30 minutes, starting 5 minutes after injection. Mean ± S.E. (n = 8–15) †$p<0.05$, significantly lower than respective control *$p<0.05$, significantly different from group-housed, ‡$p<0.05$, significant increase above activity at dose producing maximal reduction.

observations. The animal's hind paws were placed on a block 1.3 cm in height. A positive response was recorded if this posture was maintained for 30 seconds. Animals were given three trials before a negative score was recorded for that observation. Mice with two or more positive scores over the six observation times were recorded as cataleptic. Testing was conducted in an isolation room between 9 a.m. and 3 p.m.

Drugs

Apomorphine HCl (Sigma Chemical Corp., St. Louis, MO) was prepared with 0.9% saline containing 0.1% ascorbic acid. The enantiomers of 3-PPP HCl (Dr. H. Wikström, Department of Pharmacology, Organic Chemistry Unit, University of Göteborg, Sweden) were dissolved in 0.9% saline. Doses in mg/kg refer to the respective salt.

Statistics

Statistics were calculated with the Statistical Analysis System (SAS, Version 82.4) produced by the SAS Institute, Cary, NC. The General Linear Model Procedure (PROC GLM) was used for either a 2-way or 3-way analysis of variance (ANOVA) for the main effects of housing (GH vs. IH), dose and isomer, (+)- or (−)-3-PPP, followed by Newman-Keuls multiple range test. Chi-square tests were used to compare the proportion of fighters and nonfighters in control and drug-treated groups and the proportion of mice displaying catalepsy. The accepted level for significance was $p<0.05$.

RESULTS

Motor Activity Responses in Differentially-Housed Mice

Differential housing produced a significant effect on the motor activity response to (+)- and (−)-3-PPP, as shown in Figs. 1 and 2. By 3-way ANOVA of the activity counts following (+)- or (−)-3-PPP, the main effects of housing and dose were significant, $F(1,316) = 23.79$, $p<0.0001$; and, $F(7,316) = 69.20$, $p<0.0001$, respectively, but not isomer, $F(1,316) = 0.82$, $p<0.3659$. There

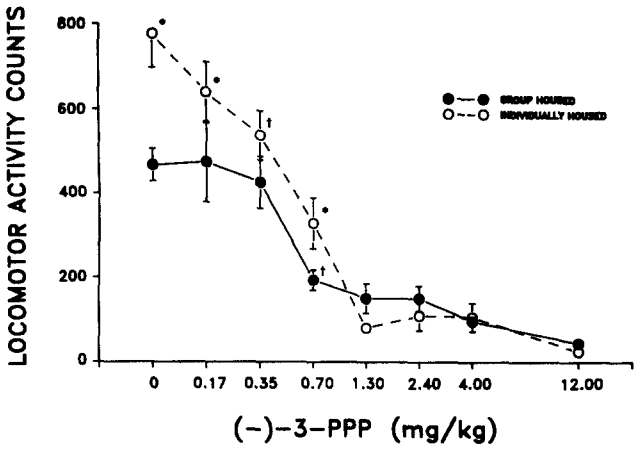

FIG. 2. Motor activity responses of differentially-housed mice to (−)-3-PPP. Mice were either group- or individually-housed for 4–5 weeks. Activity counts were recorded for 30 minutes, starting 5 minutes after injection. Mean ± S.E. (n = 8–15) †$p<0.05$, significantly lower than respective control, *$p<0.05$, significantly different from group-housed.

were no significant interactions between housing condition, dose or isomer. IH mice showed higher levels of spontaneous activity than GH mice in a novel environment (activity meter), as has been previously reported. In response to (+)-3-PPP (Fig. 1), to (−)-3-PPP (Fig. 2) and, as previously reported (38), to apomorphine, IH mice were more sensitive to the activity-reducing effects of DA agonists than GH mice, i.e., significant decreases in activity counts from the respective control groups were found with lower doses of (−)- and (+)-3-PPP in IH mice than in GH mice. The first doses at which activity counts were significantly lower than control groups were: (+)-3-PPP, 0.17 vs. 0.35 mg/kg; and (−)-3-PPP, 0.35 vs. 0.70 mg/kg, for IH and GH mice respectively. Both (+)- and (−)-3-PPP reduced activity counts to similar levels in GH and IH mice. The ED_{50}'s of these compounds to reduce motor activity in GH vs. IH mice were not significantly different (Table 1).

The ascending portion of the biphasic activity response curve to (+)-3-PPP appeared at lower doses in IH mice than in GH mice, with significant increases above the respective nadir at the doses of 4 and 12 mg/kg for IH and GH mice respectively. These results with (+)-3-PPP resemble the pattern seen with apomorphine (38). Both GH and IH mice had a monophasic activity response to (−)-3-PPP.

Fighting by Individually-Housed Mice

Table 2 summarizes the effects of apomorphine, (+)- and (−)-3-PPP on spontaneous fighting by mice individually housed for 4–5 weeks. There were no significant drug effects on the number of mice fighting with respect to control groups. However, there was a trend to a smaller number of fighters at 0.15 mg/kg apomorphine and 12 mg/kg (+)-3-PPP, doses which are associated with the onset of effects at postsynaptic DA receptors (9,13). Among those mice fighting, there were no effects of any drug on the latency to fight or the total fighting time (Table 2).

The ED_{50}'s for the inhibition of spontaneous activity in individually-housed mice, i.e., apomorphine, 0.012 mg/kg; (+)-3-PPP, 0.51 mg/kg; and (−)-3-PPP, 0.56 mg/kg, are ineffective doses for the inhibition of spontaneous fighting. Doses of the DA agonists which decreased activity counts to less than one-half the counts of the control group in 100% of the mice tested, i.e., 1.3 mg/kg (+)- or (−)-3-PPP and 0.075 mg/kg apomorphine, also did not have a significant effect on the number of mice fighting. Relative to the number of mice fighting in the respective control groups, it can be estimated that the ED_{50}'s for the inhibition of fighting would be greater than 0.075 mg/kg apomorphine, 12 mg/kg (+)-3-PPP and 2–4 mg/kg (−)-3-PPP. Although (−)- and (+)-3-PPP were equipotent in reducing motor activity, the (−) isomer appeared to be slightly more potent than the (+) isomer for inhibiting fighting. However, there is insufficient data to determine whether or not there is a significant difference between (+)- and (−)-3-PPP on fighting.

Induction of Catalepsy by (−)-3-PPP

Over the dose range of 12–24 mg/kg, (−)-3-PPP produced catalepsy in a significant proportion of IH mice, 45–75% (χ^2 =

TABLE 1

ESTIMATED ED_{50} AND 95% CONFIDENCE LIMITS (mg/kg) FOR THE INHIBITION OF SPONTANEOUS MOTOR ACTIVITY IN GROUP- AND INDIVIDUALLY-HOUSED MICE

	Group-Housed	Individually-Housed
Apomorphine	0.018(0.009–0.036)	0.012 (0.005–0.030)
(+)-3-PPP	0.50 (0.26–0.94)	0.51 (0.29–0.84)
(−)-3-PPP	1.00 (0.51–1.95)	0.56 (0.27–1.16)

TABLE 2

THE EFFECTS OF APOMORPHINE, HALOPERIDOL, (+)- OR (−)-3-PPP ON THE FIGHTING OF INDIVIDUALLY-HOUSED MICE

Dose mg/kg	Number Tested	Number Fighting	Percent Fighting	Latency to Fight* (sec)	Total Fighting Time* (sec)
Apomorphine					
Vehicle	12	9	75.0	201 ± 65	41.9 ± 8.5
0.018	12	6	50.0	220 ± 53	39.5 ± 8.1
0.038	12	7	58.3	151 ± 78	25.1 ± 3.1
0.075	12	5	41.7	123 ± 56	30.7 ± 9.2
0.15	8	2	25.0	295	31.7
(+)-3-PPP					
Vehicle	19	13	68.4	173 ± 35	36.3 ± 6.4
0.7	11	5	45.5	345 ± 39	25.1 ± 13.3
1.3	10	5	50.0	227 ± 39	17.2 ± 3.1
2.4	10	6	60.0	158 ± 32	24.6 ± 4.9
4.0	10	4	40.0	255 ± 47	25.9 ± 5.3
12.0	9	3	33.3	139 ± 83	55.7 ± 34.8
(−)-3-PPP					
0.7	11	5	45.5	160 ± 78	24.4 ± 6.6
1.3	10	4	40.0	421 ± 81	27.3 ± 13.9
2.4	9	2	22.2	351	24.4
4.0	10	3	30.0	261 ± 111	16.6 ± 8.4
12.0	10	2	20.0	102	11.6

*Mean ± S.E. from fighters.

Mice individually housed for 4–5 weeks were tested for fighting after pretreatment as described in the Method section. Control groups received the corresponding vehicle. Both isomers of 3-PPP were compared to the same control group.

TABLE 3

(−)-3-PPP-INDUCED CATALEPSY IN GROUP-HOUSED AND INDIVIDUALLY-HOUSED MICE

Dose mg/kg	% Cataleptic Group-Housed	Individually-Housed
Control	0 (12)	0 (12)
12.0	33.3 (12)	50.0* (12)
18.0	33.3 (12)	75.0* (12)
24.0	25.0 (12)	45.4* (11)
36.0	16.7 (12)	25.0 (12)

Mice were group- or individually-housed for 4–5 weeks. The number of animals tested is indicated in parentheses.

*$p<0.05$, with respect to control, Chi-Square test.

16.003, $p<0.05$), whereas only 25–33% of the GH mice were scored cataleptic ($\chi^2=5.688$, $p>0.05$) (Table 3). At 36 mg/kg, sedative effects were apparent and the percentage of mice scored positive for catalepsy was reduced. The mice that met the criteria were akinetic and maintained an abnormal posture for a minimum of 30 seconds in at least two observations over a 30-minute test period. In both groups of mice the quality of the cataleptic state resembled that seen with haloperidol, and not the rigid catatonia induced by morphine, as described by VanderWende and Spoerlein (34).

DISCUSSION

The present study demonstrates that although individually-housed mice are equally or slightly more sensitive than group-housed mice to the attenuation of spontaneous motor activity by autoreceptor-activating doses of DA agonists, this pharmacological treatment is insufficient to inhibit spontaneous fighting. These two behaviors of the "isolation syndrome," the hyperactivity in a novel environment and intermale fighting, have been associated with increased reactivity of monoaminergic systems relative to group-housed mice (4, 5, 15, 29, 32, 36). Low doses of DA agonists attenuate spontaneous activity, decrease the rate of DA cell body firing and decrease the rate of DA synthesis via interactions with DA autoreceptors (2, 6, 9, 12, 18, 19, 40). In a previous study we reported that group- and individually-housed mice differ in the motor activity response to a novel environment and to amphetamine but do not differ in a biochemical measure of DA autoreceptor sensitivity, the antagonism by apomorphine of GBL (gamma butyrolactone)-induced increases in DOPA accumulation (38), suggesting that the hyperactivity of individually-housed mice in a novel environment and the increased sensitivity to the motor stimulating effects of amphetamine are not due to subsensitivity of DA autoreceptors relative to group-housed mice. For each of the DA agonists tested in the present study, significant reductions of spontaneous activity were achieved at doses associated with effects on DA autoreceptors but without significant effects on fighting. As the doses of these drugs were increased to the range associated with the stimulation of postsynaptic DA receptors, there was a trend toward fewer mice fighting which may be a nonspecific effect due to response incompatibility with other behaviors induced in that dose range. A reduction in the preference for novelty by mice has also been associated with higher doses of apomorphine, whereas doses in the range of autoreceptor activity were ineffective (20).

In addition to the well-established behavioral and biochemical effects of (+)-3-PPP on dopaminergic function, recent data from in vitro binding experiments have shown a high affinity for *sigma* binding sites (16). However, functional correlates for sigma site interaction remain to be established. The in vivo effects of (+)-3-PPP on DA synthesis, DA cell firing and motor activity appear to be mediated by D_2 and not *sigma* receptor interactions, as demonstrated by the antagonism of these effects with the D_2 antagonist d-butaclamol but not l-butaclamol, the *sigma* selective isomer (14). The effects of (+)-3-PPP on motor activity and fighting in the present study resemble apomorphine, which is inactive or a very weak inhibitor in *sigma* binding assays (28,30). In contrast to the lack of a significant effect of (+)-3-PPP on fighting in the present study, phencyclidine (PCP) produces significant increases in spontaneous fighting by naive individually-housed mice (39). PCP and *sigma* site interactions have been shown to be distinct in in vitro binding assays (17,27), supporting the proposed nomenclature for separate PCP and *sigma* sites (26).

Previous reports have indicated that (−)-3-PPP is a partial DA agonist with properties of a DA antagonist at doses higher than those with autoreceptor agonist activity. However, (−)-3-PPP did not induce catalepsy or potentiate catalepsy induced by neuroleptics in rats (1,13). An unexpected finding of the present study was that catalepsy was present in a significant proportion of individually-housed but not group-housed mice. Individually-housed mice have also been shown to be more sensitive to the cataleptic effects of haloperidol (41). We have previously shown that individually-housed mice are more sensitive to the motor stimulant effects of apomorphine following reserpine treatment, an in vivo model of postsynaptic DA receptor sensitivity (38). These results suggest that individually-housed mice may be a more sensitive animal model for testing neuroleptic-induced catalepsy to assess the liability of these drugs for extrapyramidal side effects. The neurochemical mechanisms underlying the differential sensitivity of group- and individually-housed mice to catalepsy are not known.

In summary, the present study demonstrates that individually-housed mice are equally or slightly more sensitive than group-housed mice to the modulation of spontaneous motor activity by autoreceptor-activating doses of DA agonists. However, autoreceptor-activating effects of DA agonists are insufficient to inhibit fighting. Thus, two behavioral characteristics of individually-housed mice, hyperactivity in a novel environment and aggressive behavior, may be mediated by different neurochemical mechanisms.

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REFERENCES

1. Arnt, J.; Bøgeso, K. P.; Christensen, A. V.; Hyttel, J.; Larsen, J.-J.; Svendsen, O. Dopamine receptor agonistic and antagonistic effects of 3-PPP enantiomers. Psychopharmacology (Berlin) 81:199–207; 1983.
2. Arnt, J.; Christensen, A. V.; Hyttel, J.; Larsen, J.-J.; Svendsen, O. Effects of putative dopamine autoreceptor agonists in pharmacological models related to dopaminergic and neuroleptic activity. Eur. J. Pharmacol. 86:185–198; 1983.
3. Blanc, G.; Herve, D.; Simon, H.; Lisoprowaski, A.; Glowinski, J.;

Tassin, P. Response to stress of mesocortical-frontal dopaminergic neurones in rats after long-term isolation. Nature 284:265–267; 1980.
4. Brain, P. What does individual housing mean to a mouse? Life Sci. 16:187–200; 1975.
5. Brain, P. F.; Nowell, N. W. Some behavioral and endocrine relationships in adult male laboratory mice subjected to open field and aggression tests. Physiol. Behav. 4:945–947; 1969.
6. Costall, B.; Lim, S. K.; Naylor, R. J. Characterisation of the mechanisms by which purported dopamine agonists reduce spontaneous locomotor activity of mice. Eur. J. Pharmacol. 73:175–188; 1981.
7. Denenberg, V. H.; Gaulin-Kremer, E.; Gandelman, R.; Zarrow, M. X. The development of standard stimulus animals for mouse *(Mus musculus)* aggression testing. Anim. Behav. 21:590–598; 1973.
8. DiChiara, G.; Porceddu, M. L.; Vargiu, L.; Argiolas, A.; Gessa, G. L. Evidence for dopamine receptors mediating sedation in the mouse brain. Nature 264:564–567; 1976.
9. Feenstra, M. G. P.; Sumners, C.; Goedemoed, J. H.; deVries, J. B.; Rollema, H.; Horn, A. S. A comparison of the potencies of various dopamine receptor agonists in models for pre- and postsynaptic receptor activity. Naunyn Schmiedebergs Arch. Pharmacol. 324: 108–115; 1983.
10. Gandelman, R.; Simon, N. G.; McDermott, N. J. Prenatal exposure to testosterone and its precursors influence morphology and later behavioral responsiveness to testosterone of female mice. Physiol. Behav. 23:23–26; 1979.
11. Garattini, S.; Giacolone, E.; Valzelli, L. Biochemical changes during isolation-induced aggressiveness in mice. In: Garattini, S.; Sigg, E. B., eds. Aggressive behavior. New York: John Wiley and Sons; 1969:179–187.
12. Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D.; Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G. 3-PPP, a new centrally acting DA-receptor agonist with selectivity for autoreceptors. Life Sci. 28:1225–1238; 1981.
13. Hjorth, S.; Carlsson, A.; Clark, D.; Svensson, K.; Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A.; Nilsson, J. L. G. Central dopamine receptor agonist and antagonist actions of the enantiomers of 3-PPP. Psychopharmacology (Berlin) 81:89–99; 1983.
14. Hjorth, S.; Clark, D.; Carlsson, A. Lack of functional evidence for the involvement of sigma opiate receptors in the actions of 3-PPP enantiomers on central dopaminergic systems: discrepancies between *in vitro* and *in vivo* observations. Life Sci. 37:673–684; 1985.
15. Hodge, G. K.; Butcher, L. L. Catecholamine correlates of isolation-induced aggression in mice. Eur. J. Pharmacol. 31:81–93; 1975.
16. Largent, B. L.; Gundlach, A. L.; Snyder, S. H. Psychotomimetic opiate receptors labeled and visualized with (+)-[^{3}H]-3-(3-hydroxyphenyl)-N-(1-propyl)piperidine. Proc. Natl. Acad. Sci. USA 81: 4983–4987; 1984.
17. Largent, B. L.; Gundlach, A. L.; Snyder, S. H. Pharmacological and autoradiographic discrimination of *sigma* and phencyclidine receptor binding sites in brain with (+)-[^{3}H]SKF 10,047, (+)-[^{3}H]-3-(3-hydroxyphenyl)-N-(1-propyl)piperidine and [^{3}H]-1-[1-(2-thienyl)cyclohexyl]piperidine. J. Pharmacol. Exp. Ther. 238:739–748; 1986.
18. Martin, G. E.; Haubrich, D. R.; Williams, M. Pharmacological profiles of the putative dopamine autoreceptor agonists 3-PPP and TL-99. Eur. J. Pharmacol. 76:15–23; 1981.
19. Martin, G. E.; Bendesky, R. J. Mouse locomotor activity: an *in vivo* test for dopamine autoreceptor activation. J. Pharmacol. Exp. Ther. 229:706–711; 1984.
20. Misslin, R.; Ropartz, P.; Jung, L. Impairment of responses to novelty by apomorphine and its antagonism by neuroleptics in mice. Psychopharmacology (Berlin) 82:113–117; 1984.
21. Modigh, K. Effects of isolation and fighting in mice on the rate of synthesis of noradrenaline, dopamine and 5-hydroxytryptamine in the brain. Psychopharmacology (Berlin) 33:1–17; 1973.
22. Modigh, K. Effects of social stress on the turnover of brain catecholamines and 5-hydroxytryptamine in mice. Acta Pharmacol. Toxicol. 34:97–105; 1974.
23. Mulder, A. H.; Draper, R.; Sminia, P.; Schoffelmeer, A. N. M.; Stoof, J. C. Agonist and antagonist effects of 3-PPP enantiomers on functional dopamine autoreceptors and postsynaptic dopamine receptors *in vitro*. Eur. J. Pharmacol. 107:291–297; 1985.
24. Oehler, J.; Jahkel, M.; Schmidt, J. Inhibition of isolation-induced changes in aminergic transmission by chronic lithium treatment. Pharmacol. Biochem. Behav. 21:181–184; 1984.
25. Plantje, J. F.; Hansen, H. A.; Daus, F. J.; Stoof, J. C. The effects of SCH 23390, YM 09151-2, (+)- and (−)-3-PPP and some classical neuroleptics on D-1 and D-2 receptors in rat neostriatum in vitro. Eur. J. Pharmacol. 105:73–83; 1984.
26. Quirion, R.; Chicheportiche, R.; Contreras, P. C.; Johnson, K. M.; Lodge, D.; Tam, S. W.; Woods, J. H.; Zukin, S. R. Classification and nomenclature of phencyclidine and sigma receptor sites. Trends Neurosci. 10:444–446; 1987.
27. Sircar, R.; Nichtenhauser, R.; Ieni, J. R.; Zukin, S. R. Characterization and autoradiographic visualization of (+)-[^{3}H]SKF 10,047 binding in rat and mouse brain: further evidence for phencyclidine/"*sigma* opiate" receptor commonality. J. Pharmacol. Exp. Ther. 237:681–688; 1986.
28. Su, T.-P. Evidence for sigma opioid receptor binding of [^{3}H]SKF-10047 to etorphine-inaccessible sites in guinea pig brain. J. Pharmacol. Exp. Ther. 223:284–290; 1982.
29. Svare, B. B.; Leshner, I. Behavioral correlates of intermale aggression and grouping in mice. J. Comp. Physiol. Psychol. 85:203–210; 1973.
30. Tam, S. W.; Cook, L. Sigma opiates and certain antipsychotic drugs mutually inhibit (+)-[^{3}H]SKF 10,047 and [^{3}H]haloperidol binding in guinea pig membranes. Proc. Natl. Acad. Sci. USA 81:5618–5621; 1984.
31. Tizabi, Y.; Massari, J.; Jacobowitz, D. M. Isolation induced aggression and catecholamine variation in discrete brain areas of the mouse. Brain Res. Bull. 5:81–86; 1980.
32. Valzelli, L. The "isolation syndrome" in mice. Psychopharmacologia 31:305–320; 1973.
33. Valzelli, L.; Bernasconi, S. Aggressiveness by isolation and brain serotonin turnover changes in different strains of mice. Neuropsychobiology 5:129–135; 1979.
34. VanderWende, C.; Spoerlein, M. T. Morphine-induced catalepsy in mice. Neuropharmacology 18:633; 1979.
35. vom Saal, F. S.; Gandelman, R.; Svare, B. Aggression in male and female mice: Evidence for changed neural sensitivity in response to neonatal but not adult androgen exposure. Physiol. Behav. 17:53–57; 1976.
36. Welch, A. S.; Welch, B. L. Isolation, reactivity and aggression: evidence for an involvement of brain catecholamines and serotonin. In: Eleftheriou, B. E.; Scott, J. P., eds. The physiology of aggression and defeat. New York: Plenum Press; 1971:91–142.
37. Wilmot, C. A.; VanderWende, C.; Spoerlein, M. T. Behavioral responses to apomorphine and amphetamine in differentially housed mice. Psychopharmacology (Berlin) 84:105–108; 1984.
38. Wilmot, C. A.; VanderWende, C.; Spoerlein, M. T. Behavioral and biochemical studies of dopamine receptor sensitivity in differentially housed mice. Psychopharmacology (Berlin) 89:364–369; 1986.
39. Wilmot, C. A.; VanderWende, C.; Spoerlein, M. T. The effects of phencyclidine on fighting in differentially housed mice. Pharmacol. Biochem. Behav. 28:341–346; 1987.
40. Yarbrough, G. G.; McGuffin-Clineschmidt, J.; Singh, D. K.; Haubrich, D. R.; Bendesky, R. J.; Martin, G. E. Electrophysiological, biochemical and behavioral assessment of dopamine autoreceptor activation by a series of dopamine agonists. Eur. J. Pharmacol. 99:73–78; 1984.
41. Zetler, G. Haloperidol catalepsy in grouped and isolated mice. Pharmacology 13:526–532; 1975.