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Psychopharmacological Profile of 1-(M-(Trifluoromethyl) Phenyl) Piperazine (TFMPP)

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FRANCES, H. *Psychopharmacological profile of 1-(m-(trifluoromethyl) phenyl) piperazine (TFMPP).* PHARMACOL BIOCHEM BEHAV 31(1) 37–41, 1988.—The effect of TFMPP, an agonist of the 5-HT_{1b} receptors, was studied in mice on several psychopharmacological parameters. In contrast to imipramine-like drugs, TFMPP neither antagonized reserpine-induced hypothermia nor increased yohimbine-induced toxicity. Similarly to imipramine-like drugs, TFMPP antagonized oxotremorine-induced hypothermia and was active in the behavioural despair test. In addition, TFMPP normalized a social behavioural deficit induced by isolation. The effects of TFMPP on oxotremorine-induced hypothermia in the behavioural despair test and in the isolation-induced social behavioural deficit are all antagonized by d-l propranolol. It is concluded that TFMPP seems to possess psychotropic activity resembling only in part that of imipramine-like drugs and that these actions may be mediated through 5-HT_{1b} receptors.

TFMPP Psychopharmacology Behaviour 5-HT_{1b} receptors

AMONG numerous hypotheses, affective disorders have been linked to a deficiency in the serotonergic system in brain [5, 25, 31]. The 5-HT_2 receptors may be involved since they are down-regulated after chronic treatments with antidepressant drugs but they are up-regulated after electroconvulsive shocks [14]. The 5-HT_{1a} receptors may also be involved since buspirone, a selective agonist of 5-HT_{1a} receptors [13], improved associated depressive symptoms when administered to anxious patients [6, 11]. In addition, an open trial [28] suggests buspirone to possess a significant antidepressant effect for a nonmelancholic subgroup of depressed patients. Taken together, these results do not permit a consistent hypothesis. However, four kinds of 5-HT receptors have now been identified (5-HT_{1a}, 5-HT_{1b}, 5-HT_{1c} and 5-HT_2) and selective drugs have been developed [21]. The study of the psychopharmacological profile of such new selective drugs would possibly throw a new light on the mechanism of action of antidepressant drugs. The present study examines the psychopharmacological profile of l-(m-(trifluoromethyl) phenyl) piperazine (TFMPP). TFMPP is a selective 5-HT_1 agonist [19] with central effects [10]. McKenney and Glennon [17] demonstrated that TFMPP-stimulus generalization occurs in rats with the purported 5-HT_{1b} agonist Ru 24969 but neither with the purported 5-HT_2 agonist l-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) nor with the 5-HT_{1a} agonist 8-OH-DPAT. The selectivity of TFMPP at the 5-HT_{1b} site has been reported using binding experiments [1, 13, 29].

The effects of TMFPP have been investigated in the following battery of tests used for evaluating antidepressant activity. The reserpine model [2, 4, 20] was chosen because it is the most used in the screening of antidepressant drugs. Oxotremorine antagonism is also frequently employed. Oxotremorine is a cholinomimetic drug and it has long been thought that imipramine-like drugs antagonized the effects of oxotremorine administration through their anticholinergic properties [32]. However, oxotremorine-induced hypothermia is antagonized not only by drugs with anticholinergic properties but also by beta-noradrenergic and serotonergic agents [7] and therefore, can be considered as a more generally valid test for antidepressant activity.

Another frequently used test is the yohimbine potentiation test, the toxicity of yohimbine in mice being increased by imipramine-like drugs and other atypical antidepressants [18,26]. The behavioural despair test in which mice or rats are forced to swim in water from which they cannot escape is sensitive to antidepressants and stimulant drugs [22]. The social behavioural deficit is a more recently described test [9]. Its meaning is not clearly established but it seems to be sensitive to stimulants of the 5-HT_{1b} receptors.

METHOD

Animals

Male Swiss NMRI mice (20–24 g) from C.E.R.J. Genest St. Isle 53940 France, were used in all experiments except in the despair test in which Swiss CD Charles River male mice (20–24 g) from St. Aubin les Elbeufs 76140 France were used. Mice were housed in groups of 10 with a 12 hours light-dark schedule in a room thermostatically maintained at 21±1°C. In the experiments with isolated mice, the animals

TABLE 1

DECREASE IN SPONTANEOUS MOTOR ACTIVITY INDUCED BY TFMPP BETWEEN THE 30th AND THE 60th MINUTE AFTER ITS ADMINISTRATION

TFMPP mg/kg	Number of Light Beams Crossed mean ± S.E.M.
0	456.5 ± 29.2
2	428.7 ± 35.0 N.S.
4	405.1 ± 28.6 N.S.
8	323.5 ± 43.7*

$F(3,44)=2.74$, $p<0.05$.
N.S.: nonsignificant, *$p<0.05$.

TABLE 2

DECREASE IN RECTAL TEMPERATURE INDUCED BY TFMPP 30 MINUTES AFTER ITS ADMINISTRATION

TFMPP mg/kg	Mean Rectal Temperature °C ± S.E.M.
0	37.8 ± 0.2
2	37.7 ± 0.1 N.S.
4	36.6 ± 0.3*
8	36.0 ± 0.2†

$F(3,33)=9.83$, $p<0.001$.
N.S.: nonsignificant, *$p<0.01$, †$p<0.001$.

were singly housed one in 20×10×10 cm cages, other conditions being unchanged. Food and water were freely available.

Spontaneous motor activity was measured in a photocell activimeter, one animal per cage [3], between the 30th and the 60th minutes following the injections. Twelve animals were used in each group. Rectal temperatures were measured using a thermosensitive probe inserted to constant depth. The number of mice used varied from 7 to 14 in each group.

Interaction With Reserpine

Reserpine (2.5 mg/kg) was administered by intraperitoneal route (IP) to mice housed together in their usual cages [8]. Rectal temperature was measured 3 hours after reserpine and mice were allotted to groups in such a manner that the mean rectal temperature was the same in each group of 12 mice. TFMPP (or demineralized water for controls) was administered 4 hours after reserpine. Rectal temperature was measured, the presence of akinesia observed and ptosis scored (form 0 to 4) [27] every 30 minutes for 2 hours.

Interaction With Oxotremorine

TFMPP or demineralized water were adminstered 30 minutes before oxotremorine (0.5 mg/kg, IP). Tremors were scored on a scale of 1 to 3 (3: continuous tremors; 2: intermittent tremors, but tremors always appeared when mice were moving; 1: no apparent tremors, but when the mice were hung up by the tail, tremors appeared and the forepaws crossed) and presence or absence of akinesia was observed 10, 20, 30, 60, 90 and 120 minutes after oxotremorine. The appearance of tears, hypersalivation and defecation was observed and the rectal temperature measured every 30 minutes for 2 hours [30]. Eleven or 12 mice were used in each group.

Potentiation of Yohimbine-Induced Toxicity

The subcutaneous administration of yohimbine (25 mg/kg) causes on average one death out of ten mice [18,26]. Potentiation of this toxicity by TMFPP was investigated by administering the drug 30 minutes before yohimbine.

Depair Test

For this test, Swiss CD Charles River Male mice were used because Porsolt *et al.* [24] showed that the strain of mice that we used in the other tests were unsuitable in the behavioural despair test. Thirty minutes after TFMPP administration, a mouse was introduced into a transparent glass vessel (25 cm high, 10 cm diameter) containing 10 cm water (21–23°C). After 2 minutes of habituation to the water, the total duration of immobility was measured between the second and the sixth minute. Ten mice were used in each group.

Social Behavioural Deficit

Mice were isolated for one week. Then an isolated mouse and a group-housed mouse were put together under an inverted beaker (15 cm diameter) and the number of escape attempts for each mouse was observed during 2 minutes. An escape attempt is defined in the following way: (1) the two forepaws are leaned against the beaker wall, or (2) the mouse sniffs the beak of the beaker, or (3) the mouse scratches the glass floor. There is no minimal duration for one attempt. If one attempt lasted more than 3 seconds, it was considered as 2 attempts.

TFMPP (or demineralized water for controls) was administered only to the isolated mice 30 minutes before the test. For each pair of mice, the difference of the scores: group-housed mouse − isolated mouse was calculated. The results are expressed as the mean difference between the scores of group-housed and isolated mouse for 10 pairs of mice in each group.

D-1 propranolol was administered 15 minutes before water or TFMPP in all cases.

Drugs

Drugs used were: oxotremorine base and 1-(m-(trifluoromethyl) phenyl) piperazine hydrochloride (TFMPP) (Aldrich Chemical Co., Inc., Milwaukee, WI); reserpine and yohimbine hydrochloride (Sigma, St. Louis, MO); d-l propranolol hydrochloride (ICI Pharma, Cergy, France).

TFMPP, d-l propranolol and demineralized water were adminstered intraperitoneally. Except reserpine, all drugs were dissolved in demineralized water or suspended in arabic gum. Reserpine, first dissolved in acetic acid and kept cool (0°C), was dissolved in demineralized water just before use. All drugs were administered in a volume of 0.25 ml/20 g body weight. The doses are expressed as the salts.

Data were analyzed for statistical significance using the one-way analysis of variance followed by the *t*-test.

RESULTS

Spontaneous motor activity was unchanged with the doses of 2 and 4 mg/kg of TFMPP and decreased with 8 mg/kg (Table 1).

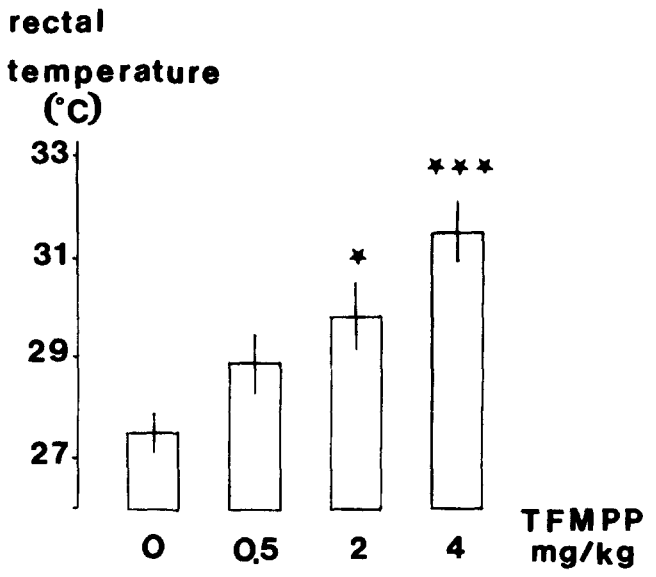

FIG. 1. Dose-dependent antagonism of oxotremorine-induced hypothermia measured 90 minutes after TFMPP administration. The results are the mean rectal temperature (±S.E.M.). One-way analysis of variance, $F(3,43)=5.89$, $p<0.01$; ★★$p<0.05$; ★★★$p<0.001$.

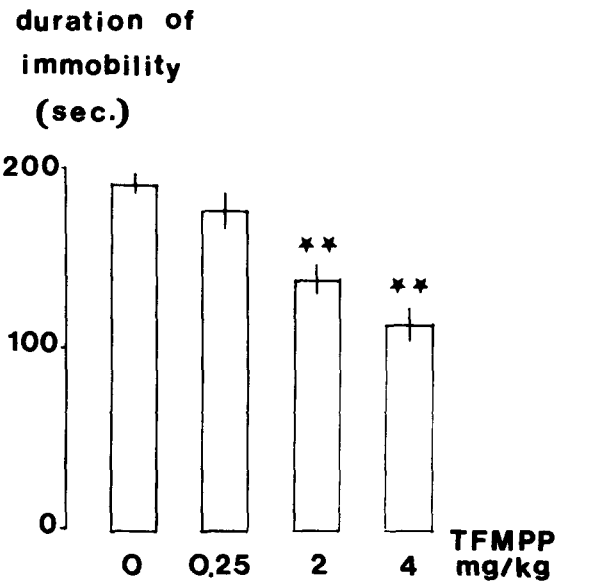

FIG. 2. Dose-dependent decrease in the duration of immobility induced by TFMPP in the behavioural despair test. Results are the mean±S.E.M. One-way analysis of variance, $F(3,36)=4.51$, $p<0.01$; ★★$p<0.001$.

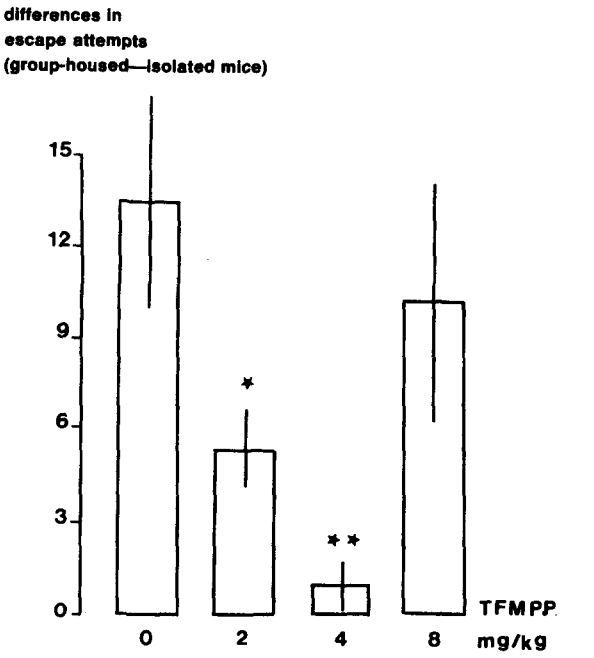

FIG. 3. Effect of TFMPP in the social behavioural deficit test. The ordinate represents the mean difference (±S.E.M.) between the scores of the group-housed and the isolated mice. One-way analysis of variance, $F(3,46)=2.95$, $p<0.05$; ★$p<0.05$; ★★$p<0.01$.

The rectal temperature was significantly decreased from 4 mg/kg (Table 2). The yohimbine-induced toxicity was unmodified by TFMPP at the doses of 0.25, 0.5 or 2 mg/kg. The hypothermia induced by reserpine was not antagonized by TFMPP but, on the contrary, dose-dependently increased. The rectal temperature of reserpinized mice, 60 minutes after the treatment with TFMPP, was (°C±S.E.M.): controls, 33.0±0.3; 0.2 mg/kg, 31.9±0.4; 2 mg/kg, 29.4±0.3. Ptosis and akinesia were unchanged whatever the time of measurement.

TABLE 3

COMPARISON OF THE EFFECTS OF TFMPP AND IMIPRAMINE IN A BATTERY OF BEHAVIOURAL AND PHARMACOLOGICAL TESTS

Tests	TFMPP	Imipramine
Behavioural despair	+	+
Social behavioural deficit	+	0
Antagonism of reserpine hypothermia	0	+
Antagonism of oxotremorine hypothermia	+	+
Potentiation of yohimbine-induced toxicity	0	+

Oxotremorine-induced hypothermia was dose-dependently antagonized by TFMPP, the lowest active dose being 2 mg/kg (Fig. 1). Neither central (tremors, akinesia) nor peripheral (lachrymation, salivation, defecation) signs of cholinergic stimulation were altered.

In the despair test (Fig. 2), the duration of immobility was reduced by TFMPP. One week of isolation induced, in mice, a reduction in the number of escape attempts: this is the so-called "isolation-induced social behavioural deficit." The mean scores of the control mice was for group-housed mice: 23.8±1.9, for isolated mice: 10.2±2.3. The mean of the differences calculated for each pair was 13.6±3.6. TFMPP significantly reduced this difference with the doses of 2 and 4 mg/kg (Fig. 3) by increasing the number of escape attempts of the isolated mice.

The results obtained with TFMPP in these behavioural and pharmacological tests are compared to the effects of

TABLE 4

INTERACTION OF PROPRANOLOL WITH TFMPP

Treatments mg/kg	Oxotremorine Hypothermia °C (mean ± S.E.M.)	Behavioural Despair Duration of Immobility sec (mean ± S.E.M.)	Social Behavioural Deficit Difference in Escape Attempts (mean ± S.E.M.)
Water + water	27.5 ± 0.5 (6)	146.6 ± 10.4 (9)	13 ± 2.2 (10)
Water + TFMPP*	30.2 ± 0.3 (5)[b]	79.7 ± 13.8 (10)	−3.6 ± 4.3 (8)[c]
Propranolol + water*	26.7 ± 0.2 (6) N.S.	136.4 ± 19.6 (9) N.S.	11.1 ± 3.4 (10) N.S.
Propranolol* + TFMPP	26.4 ± 0.3 (6)[c1]	122.6 ± 12.4 (10)[a1]	7.6 ± 3.5 (10)[b1]
F	19.13 (3–19) $p<0.001$	4.26 (3–34) $p<0.05$	4.43 (3–34) $p<0.05$

*The dose of TFMPP was 4 mg/kg in each test. The doses of propranolol were 16 mg/kg in the behavioural despair test and 4 mg/kg in each of the other tests.

(n): number of mice or of pairs of mice (behavioural deficit).

[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$.

[1]The significance is related to the group water + TFMPP. In all other cases the significance is related to the group water + water.

imipramine in the same tests in a synaptic table (Table 3). It appears that two effects only are common to imipramine and TFMPP.

Interactions With d-l Propranolol (Table 4)

For each of the following tests: oxotremorine hypothermia, behavioural despair and social behavioural deficit, d-l propranolol administered 15 minutes before TFMPP antagonized the effects of TFMPP at a dose which was devoid of effects by itself.

DISCUSSION

The spontaneous motor activity of mice decreased with the highest dose studied of TFMPP. This result is consistent with the dose-dependent reduction in locomotor activity produced by TFMPP [15] and other piperazine-type compounds in rats. The decrease in rectal temperature observed from 4 mg/kg may, however, represent a physiological disturbing factor which may interfere with the different behaviours observed, more particularly with the pharmacological tests involving the measure of temperature. The antagonism of oxotremorine hypothermia is consistent with previous results from this laboratory demonstrating that drugs stimulating the beta-adrenergic or the serotonergic system antagonized oxotremorine hypothermia [7]. The absence of antagonism of reserpine hypothermia by TFMPP is in accordance with the finding that this hypothermia reflects merely the lack of stimulation of beta-adrenergic receptors [4,8]. Regarding the behavioural despair procedure, TFMPP is significantly active at 2 and 4 mg/kg. On the behavioural despair test, several serotonergic agonists [12,23] and antagonists [16] have been tested. Fenfluramine, primarily a serotonin releaser, is active but interacts also with noradrenergic and dopaminergic systems [12]. TFMPP is, at present, known to bind preferentially with 5-HT_{1b} receptors. It may be therefore that this binding site is involved in the despair test. The social behavioural deficit induced by isolation is completely reversed by 2 and 4 mg/kg TFMPP.

Although the dose of 8 mg/kg is inactive perhaps because of the induction of nonspecific effects, the ability of TFMPP to reverse the social behavioural deficit may well result from the stimulation of 5-HT_{1b} receptors since it is shared by Ru 24969, another agonists at these receptors [9].

The effects of TFMPP on oxotremorine hypothermia, in the behavioural despair test and in the isolation-induced social behavioural deficit, are antagonized by d-l propranolol in a significant manner. Propranolol is primarily a beta-adrenergic blocking drug. However, if d-l propranolol was acting through its beta-adrenergic properties, an opposite action of beta-adrenergic stimulants would be expected in these tests. This does not appear to be the case, for example, clenbuterol a beta-2 adrenergic agonists antagonizes oxotermorine-induced hypothermia but does not affect the social behavioural deficit or immobility in the behavioural despair test. Furthermore, beta-adrenergic stimulants antagonize reserpine-induced hypothermia [8] but TFMPP did not. It seems likely therefore that the effects of TFMPP and their antagonism by d-l propranolol are not exerted through beta-adrenergic receptors but probably through 5-HT_{1b} receptors in these tests.

It can be concluded that TFMPP is active in some behavioural and pharmacological tests and seems to possess some antidepressant activity. Its profile of action differs however from that of tricyclic antidepressants in that it has no activity on reserpine hypothermia and yohimbine-induced toxicity, but has, however, some similarities in that it is active on oxotremorine hypothermia and in the despair test. The effects of TFMPP seem most likely to be due to the stimulation of 5-HT_{1b} receptors since they are antagonized by d-l propranolol. It is suggested that further studies are needed with similar substances to ensure that they all possess common profile. If such was the case, this type of substance may possibly be useful for treating some types of depression.

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