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REPEATED TREATMENT WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS BUT NOT ANXIOLYTICS PREVENTS THE STRESS-INDUCED DEFICIT OF FIGHTING BEHAVIOR

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Repeated treatment with antidepressants but not anxiolytics prevents the stress-induced deficit of fighting behavior. G. OSSOWSKA, I. ŻEBROWSKA-ŁUPINA, Z. DANILCZUK, B. KLENK-MAJEWSKA. Pol. J. Pharmacol., 2002, 54, 373–380.

Several animal models of "depression" have been examined. One of them is chronic unpredictable stress (CUS)-induced deficit of fighting behavior in rats. In the present study, we compared the effects of two antidepressants (fluoxetine or fluvoxamine) and three anxiolytics (buspirone, lorazepam or oxazepam) on the electric footshock-induced fighting behavior in the pairs of male Wistar rats exposed to CUS procedure (16-day application of various unpredictable stressors). It was found that, in chronically stressed rats, the number of fighting attacks was significantly reduced (by about 70%). Prolonged (for 14 days) treatment of rats with fluoxetine or fluvoxamine (both at the dose of 10 mg/kg/day) counteracted the deficit of aggression induced by the chronic stress. On the contrary, the anxiolytics: lorazepam (0.5 mg/kg/day), oxazepam (5 mg/kg/day) or buspirone (0.2 mg/kg/day) administered for 14 days, did not modify the deficit of fighting induced by CUS procedure. It must be underlined that prolonged treatment with all used drugs did not change the intensity of fighting in normal (unstressed) rats. In conclusion, prolonged treatment with antidepressant drugs prevents the CUS-induced deficit of fighting behavior, whereas no beneficial effect of anxiolytic agents was found.

Key words: *fluoxetine, fluvoxamine, buspirone, lorazepam, oxazepam, chronic unpredictable stress (CUS), electric footshock-induced fighting behavior, rats*

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INTRODUCTION

It is well established that chronic stress is an important factor not only in the etiology of some somatic diseases but is also a predisposing and precipitating factor in the onset of psychiatric disorders [1, 24, 43].

Animal research has adopted this view on the relationship between stress and behavioral disorders. It was shown that chronic stress was able to evoke behavioral changes (motor activity deficit, reduced food and water consumption and decrease in responsiveness to rewarding stimuli) resembling clinical symptoms of human depression [19, 21, 22, 44]. Exposure to stressful experiences is used to induce abnormal behavior serving as models of "depression" in animals [21, 22, 43, 44]. Recently, we have reported that in the rats subjected to chronic unpredictable stress procedure (CUS) the footshock-induced fighting behavior was significantly reduced [29, 45, 46]. It was also shown that the prolonged treatment with tricyclic antidepressants prevented this behavioral deficit induced by CUS [45, 46].

Benzodiazepines represent the class of anxiolytics potentiating γ-aminobutyric acid (GABA)-mediated inhibition *via* the increase in the affinity of GABA for the GABA-A receptor complex. They are drugs of choice for the treatment of anxiety and are the most often prescribed in stressful conditions. However, prolonged treatment with benzodiazepines leads to the development of addiction, dependence and withdrawal syndrome upon abrupt discontinuation [36].

Abnormalities of serotonergic (5-HT) system have been reported in depression [3, 30]. Recently, several postmortem studies have shown that a number of 5-HT_2 receptor sites was increased in the frontal cortex of depressed patients and of suicide victims [2, 25].

Numerous observations (experimental and clinical evidence) support the notion that the brain 5-HT system is linked not only to the biological basis of depression and anxiety [11, 12, 20] but also to the mechanism of action of antidepressants and novel anxiolytics, i.e. 5-HT_{1A} receptor agonists. One of them, buspirone is the effective anxiolytic, which is devoid of the typical side effects associated with benzodiazepines such as a muscle relaxation, sedation, potential withdrawal syndrome upon discontinuation or unsafe interaction with alcohol [13, 18, 41].

In the present paper, we have compared the effects of two antidepressants: fluoxetine or fluvoxamine with three anxiolytics: buspirone, lorazepam or oxazepam on the fighting behavior deficit induced by CUS procedure in rats.

MATERIALS and METHODS

The experiments were carried out on male Wistar rats (180–220 g) kept under standard laboratory conditions with free access to food and water. The rats were housed six to a cage. All procedures were performed between 8.00 and 14.00 h.

Chronic unpredictable stress procedure

CUS was a variant of Katz et al. method [22, 23]. The rats were subjected once a day to the following kinds of unpredictable stressors: 20 s exposure to electric footshock (3 mA, impuls duration 0.2 s, every 2 s), 2 h period of immobilization at 20°C or at 4°C, 5 min exposure to electric bell, 3 min period of swimming in cold water (12°C) or 5 min period of illumination (80 ± 1 klx) and 48 h period of food deprivation. Each stressor was repeated 2 times during the 16-day stress procedure [45, 46].

Footshock-induced fighting behavior

Footshock-induced fighting behavior was elicited in rats according to Tedeschi et al. [39]. The pairs of male rats were placed in the glass cylinder (15 × 23 cm) on the steel gride floor for 10 min adaptation. Next, fighting was induced by electric footshock (intensity 3 mA, impulse duration 0.3 s rate 1/s). The number of attacks (biting, boxing, fighting) were scored during 5 min after painful stimulation. The 19–22 days before the final test, the pairs of rats have been tested for the fighting behavior and only pairs of rats having similar number of fighting attacks have been chosen for further experiments. The footshock-induced fighting behavior test was performed 49 h after the last session of CUS.

Exploratory activity

Exploratory activity (the number of squares traversed and rearings) was observed for 3 min in the open field [15], always 15 min before the fighting behavioral test.

Drugs

Drugs used were: fluoxetine (Eli Lilly, England), fluvoxamine (Duphar, France), oxazepam and lorazepam (Polfa, Poland) and buspirone (Bristol-Myers Squib, France). All drugs were injected intraperitoneally (*ip*) at a single dose 1 h before the test of fighting behavior or for 14 days, once daily, 1 h before the stressful stimulation. In stressed and unstressed rats the last dose of drug was injected 49 h before the fighting behavioral test.

Statistics

The results were statistically assessed by the Mann-Whitney U-test to compare each of the treatment with respective control. All the data are expressed as means ± SEM.

RESULTS

Effect of fluoxetine or fluvoxamine given at a single dose on footshock-induced fighting behavior and exploratory activity in rats

In control (unstressed) pairs of rats, the mean number of fighting attacks was about 140/5 min.

In rats submitted to CUS procedure, the number of fighting attacks was significantly reduced (by about 70%) when observed 48 h after the last stressor (Fig. 1).

Exploratory activity was not changed in these rats (Tab. 1).

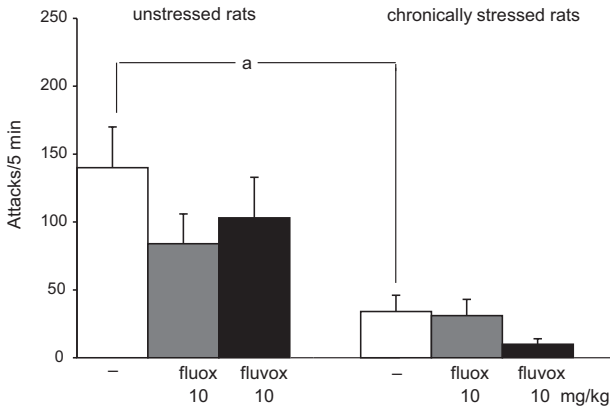

Fig. 1. The effect of fluoxetine or fluvoxamine given at a single dose on footshock-induced fighting behavior in stressed and unstressed rats. Fluoxetine (fluox) or fluvoxamine (fluvox) were administered 1 h before the test. [a] $p < 0.02$ (Mann-Whitney U-test); 6 pairs of rats were used per group

Fluoxetine and fluvoxamine, given at a single dose (10 mg/kg) influenced the intensity of fighting neither in normal nor in chronically stressed rats (Fig. 1).

Fluvoxamine but not fluoxetine significantly increased the number of squares traversed (by about 50%) in normal and rearings (by about 100%) in chronically stressed rats (Tab. 1).

Table 1. The effect of fluoxetine, fluvoxamine, buspirone, lorazepam and oxazepam given at a single dose on exploratory activity in stressed and unstressed rats

Treatment mg/kg *ip*	Squares traversed (mean ± SEM)	Rearings (mean ± SEM)
vehicle	19.8 ± 1.7	3.9 ± 0.5
stress	16.1 ± 1.5	3.6 ± 0.6
fluoxetine 10.0	15.8 ± 1.6	4.0 ± 0.7
stress + fluoxetine 10.0	14.5 ± 2.0	3.6 ± 0.5
vehicle	22.3 ± 2.2	3.3 ± 0.7
stress	21.0 ± 2.5	3.0 ± 0.5
fluvoxamine 10.0	34.1 ± 3.6[b]	4.6 ± 0.5
stress + fluvoxamine 10.0	20.5 ± 6.1	5.8 ± 1.1[d]
vehicle	20.5 ± 2.3	4.1 ± 0.7
stress	22.5 ± 4.1	4.8 ± 1.0
buspirone 0.2	18.8 ± 2.3	4.5 ± 0.7
stress + buspirone 0.2	19.0 ± 3.5	4.7 ± 1.0
vehicle	15.5 ± 1.2	4.5 ± 0.7
stress	16.8 ± 2.7	4.2 ± 1.0
lorazepam 0.5	16.4 ± 4.3	1.3 ± 0.4[a]
stress + lorazepam 0.5	15.2 ± 3.0	1.8 ± 0.5[d]
vehicle	22.3 ± 2.2	3.3 ± 0.7
stress	21.0 ± 2.5	3.0 ± 0.5
oxazepam 5.0	24.0 ± 0.4	3.3 ± 0.4
stress + oxazepam 5.0	38.5 ± 6.0[d]	6.3 ± 0.6[c]

The drugs were administered at a single dose 45 min before the test. [a] $p < 0.001$, [b] $p < 0.01$ vs. vehicle, [c] $p < 0.001$, [d] $p < 0.01$ vs. stressed control (Mann-Whitney U-test); 12 rats were used per group

Effect of prolonged treatment with fluoxetine or fluvoxamine on the footshock-induced fighting behavior and exploratory activity in rats

Neither fluoxetine nor fluvoxamine administered for 14 days (10 mg/kg/day) changed the aggressiveness of normal (unstressed) rats (Fig. 2).

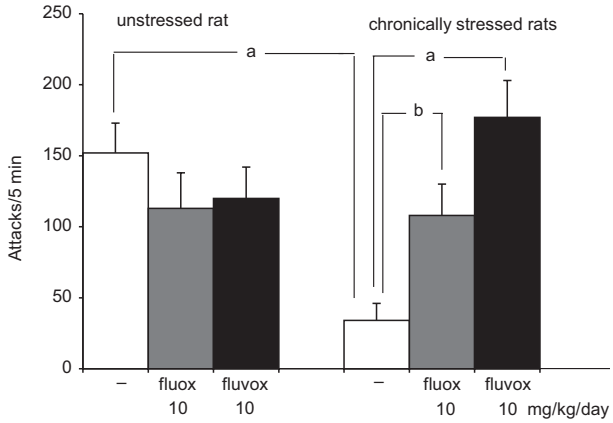

Fig. 2. The effect of prolonged treatment with fluoxetine or fluvoxamine on footshock-induced fighting behavior in stressed and unstressed rats. Fluoxetine (fluox) or fluvoxamine (fluvox) were administered *ip*, once daily for 14 days (in stressed rats 1 h before every stress session). The last dose of drug was injected 49 h before the test. [a] $p < 0.01$, [b] $p < 0.05$ (Mann-Whitney U-test); 6 pairs of rats were used per group

On the contrary, in rats exposed to chronic stress, prolonged treatment with fluoxetine or with fluvoxamine increased the number of fighting attacks when compared with the control stressed rats (Fig. 2).

Fluoxetine, but not fluvoxamine, given for 14 days, significantly increased the number of squares traversed and rearings (by about 100%) in chronically stressed rats. Neither fluoxetine nor fluvoxamine given chronically changed the exploratory activity in normal (unstressed) rats (Tab. 2).

Effect of buspirone, lorazepam or oxazepam given at a single dose on footshock-induced fighting behavior and exploratory activity in rats

Nonbenzodiazepine anxiolytic, buspirone, given at a single dose (0.2 mg/kg), changed the intensity of fighting and exploratory activity neither in normal (unstressed) nor in chronically stressed rats (Fig. 3, Tab. 2).

Benzodiazepine derivative, lorazepam (but not oxazepam), given at a single dose of 0.5 mg/kg significantly decreased the number of fighting attacks (by about 80%) in normal but not in stressed rats (Fig. 3).

Significant decrease in the number of rearings (by about 60–70%) was observed in the normal and in the chronically stressed rats receiving lorazepam (0.5 mg/kg) (Tab. 1).

Table 2. The effect of prolonged treatment with fluoxetine, fluvoxamine, buspirone, lorazepam and oxazepam on exploratory activity in stressed and unstressed rats

Treatment mg/kg *ip*	Squares traversed (mean ± SEM)	Rearings (mean ± SEM)
vehicle	18.6 ± 1.7	3.8 ± 0.7
stress	15.3 ± 2.4	3.4 ± 0.9
fluoxetine 10.0	20.3 ± 2.6	3.5 ± 0.8
stress + fluoxetine 10.0	31.1 ± 3.8[a]	7.2 ± 1.1[b]
vehicle	19.8 ± 1.7	3.9 ± 0.5
stress	16.1 ± 1.5	3.6 ± 0.6
fluvoxamine 10.0	15.0 ± 3.5	3.8 ± 0.6
stress + fluvoxamine 10.0	16.3 ± 1.7	3.3 ± 0.6
vehicle	20.5 ± 2.3	4.1 ± 0.7
stress	22.5 ± 4.1	4.8 ± 1.0
buspirone 0.2	15.8 ± 3.4	4.5 ± 1.2
stress + buspirone 0.2	19.8 ± 4.3	4.9 ± 0.8
vehicle	15.5 ± 1.2	4.5 ± 0.7
stress	18.8 ± 2.7	4.2 ± 1.0
lorazepam 0.5	14.2 ± 1.9	3.2 ± 0.6
stress + lorazepam 0.5	19.0 ± 3.1	4.1 ± 0.9
vehicle	18.6 ± 1.7	3.8 ± 0.7
stress	15.3 ± 2.4	3.4 ± 0.9
oxazepam 5.0	19.1 ± 2.7	5.2 ± 0.8
stress + oxazepam 5.0	15.8 ± 2.3	4.9 ± 1.1

The drugs were administered, once daily, for 14 days (in stressed rats 1 h before every stress session). The last dose of a drug was injected 48 h 45 min before the test. [a] $p < 0.01$, [b] $p < 0.02$ vs. stressed control (Mann-Whitney U-test); 12 rats were used per group

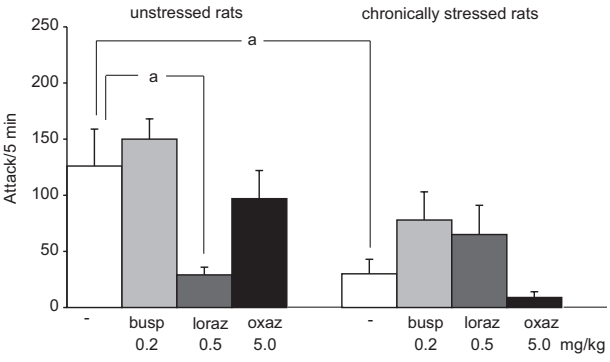

Fig. 3. The effect of buspirone, lorazepam or oxazepam given at a single dose on footshock-induced fighting behavior in stressed and unstressed rats. Buspirone (busp), lorazepam (loraz) or oxazepam (oxaz) were administered *ip* 1 h before the test. [a] $p < 0.01$ (Mann-Whitney U-test); 6 pairs of rats were used per group

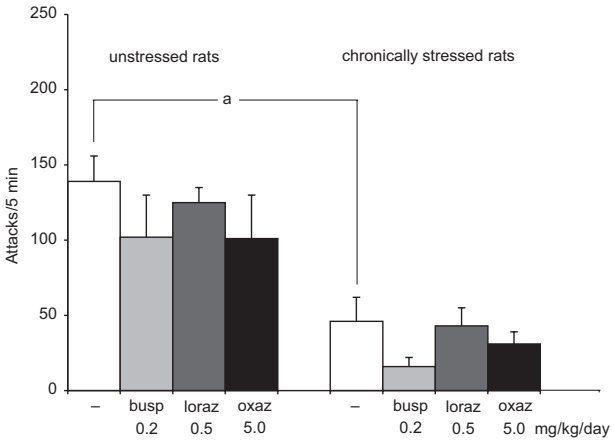

Fig. 4. The effect of prolonged treatment with buspirone, lorazepam or oxazepam on footshock-induced fighting behavior in stressed and unstressed rats. Buspirone (busp), lorazepam (loraz) or oxazepam (oxaz) were administered *ip*, once daily, for 14 days (in stressed rats 1 h before every stress session).The last dose of drug was injected 49 h before the test. [a] $p < 0.02$ (Mann-Whitney U-test); 6 pairs of rats were used per group

In rats exposed to chronic stress oxazepam given at a single dose (5 mg/kg), significantly increased the number of squares traversed and rearings (Tab. 1).

Effect of prolonged treatment with buspirone, lorazepam or oxazepam on footshock-induced fighting behavior and exploratory activity in rats

Buspirone (0.2 mg/kg/day), lorazepam (0.5 mg/kg/day) and oxazepam (5 mg/kg/day) given chronically (for 14 days) changed the intensity of fighting behavior or exploratory activity neither in control (unstressed) nor in rats exposed to chronic stress.(Fig. 4, Tab. 2).

DISCUSSION

The present study reveals that the rats exposed to CUS procedure show the reduced number of fighting attacks by about 70%. This phenomenon did not depend on locomotor activity level and was highly reproducible. The results are consistent with previous studies from our laboratory [29, 45, 46].

We have demonstrated previously that the tricyclic antidepressants given chronically (1 h before every stress session) counteracted the fighting behavior deficit induced by CUS procedure [45, 46].

In the present paper, we have shown that the prolonged treatment with antidepressant drugs, of another class, the selective 5-HT reuptake inhibitors (SSRI), fluoxetine and fluvoxamine [6, 7], similarly to tricyclic antidepressants [45, 46], restored the aggressiveness to normal level in chronically stressed rats.

The antidepressant-like activity of fluoxetine and fluvoxamine was also shown in other animal models of "depression" [27, 35].

Unlike the used antidepressants, neither buspirone, nor lorazepam or oxazepam, administered chronically, prevented the fighting behavior reduction induced by CUS procedure.

The results of the present study are consistent with the report of Sherman et al. [35] indicating that chronic administration of antidepressants effectively attenuated the "learned helplessness" behavior (another model of "depression"), but anxiolytics were inactive in this test. Our findings confirm also Muscat at al.[27] observations that fluoxetine, but not chlordiazepoxide, administered chronically reversed the stress-induced anhedonia. Nankai et al. [28] have also shown in the "learned helplessness" model, that repeated administration of anxiolytic drug, diazepam, did not produce the recovery from the deficit of performance.

It must be underlined that the effect of chronic treatment with fluoxetine, observed in this study, "normalizing" the fighting behavior in chronically stressed rats, was accompanied by locomotor stimulation, unlikely to fluvoxamine or other antidepressants described in our previous papers [29, 45, 46]. In animal models, fluoxetine appears to be a specific and selective (with regard to its acute biochemical pharmacology) inhibitor of 5-HT uptake, not affecting other neurotransmitters and receptors [6]. However Muscat et al. [27] have shown that racloprid, a specific dopamine (DA) D_2 receptor antagonist [9] reversed the therapeutic effects of fluoxetine in the chronic mild stress paradigm, suggesting the role of DA system in the effect of chronic fluoxetine treatment. Moreover, the results of Tanda et al. [37] indicate that SSRI increase extracellular DA in the prefrontal cortex and suggest that stimulation of DA transmission in this area plays a role in their antidepressant properties. So the participation of DA in the locomotor stimulatory effect of fluoxetine, observed in this study, is possible.

The present and other our studies [45, 46] have revealed that the behavioral disturbances following exposure to chronic stress (decrease in footshock-induced fighting behavior) are sensitive to chronic antidepressant treatment, but not to benzodiazepine or nonbenzodiazepine anxiolytics. It is also suggested that the lack of the effect of anxiolytics in the models of "depression" may be explained by the mechanisms underling the action of these drugs which are different from those of antidepressants.

The recovery of aggressiveness to normal level in stressed rats after chronic treatment with clinically active antidepressants, fluoxetine and fluvoxamine, suggests a role of the brain 5-HT and/or DA [27, 37] in prevention of behavioral deficits induced by the chronic stress.

Buspirone, the partial 5-HT_{1A} receptor agonist [13, 41], was introduced in the late 1980s as a novel therapeutic agent for the treatment of anxiety [4]. Moreover, it is also clinically effective antidepressant [14, 32, 33]. Therapeutic efficacy of buspirone can be seen after a period of chronic treatment [34, 38]. Studies have shown a lack of affinity of buspirone for the benzodiazepine-GABA receptor complex [5, 40]. The majority of the available studies suggest that buspirone exerts its therapeutic effects through 5-HT_{1A} receptor activation [17]. However, Pich and Samanin [31] suggested DA system involvement in the anxiolytic effect of buspirone, the suggestion supported by antagonistic affinity of buspiron for the D_2 receptor [26].

Buspirone has been reported to be active in some animal tests/models of "depression". It has been shown to decrease immobility time in the forced swimming test [10, 42] or to reduce "learned helplessness" [16].

The lack of facilitatory effect of buspirone on fighting behavior in chronically stressed rats in spite of effectiveness of the remaining drugs activating 5-HT system (fluoxetine and fluvoxamine) might be probably explained by its diverse influence upon the DA system [26, 27, 31, 37].

There is evidence that shock-induced fighting behavior is a kind of affective aggression, primarily defensive in nature [8]. The reduction of this kind of aggression seems to be specific effect of chronic stress [29, 45, 46].

Based on our and other [27–29, 35, 45, 46] findings, it may be concluded that fluoxetine and fluvoxamine, similarly to tricyclic antidepressants, administered chronically, may prevent the defensive reaction deficit induced by the chronic stress, and that 5-HT system (beside other neurotransmitters) may be involved in this effect of antidepressant treatment.

On the contrary, the anxiolytic drugs seems to be ineffective in prevention of "depressive" reactions induced by the chronic stress.

REFERENCES

1. Anisman H., Zacharko R.M.: Pharmacological biochemical and behavioral analyses of depression: animal models. In: Animal Models of Depression. Eds. Koob G.F., Ehlers C.L., Kupfer D.J., Birkhäuser, Boston 1989, 204–238.
2. Arora R.C., Meltzer H.Y.: Serotonergic measures in the brains of suicide victims: 5-HT_2 binding sites in the frontal cortex of suicide victims and control subjects. Amer. J. Psychiat., 1989, 146, 730–736.
3. Arora R.C., Meltzer H.Y.: Increased serotonin$_2$ (5-HT_2) receptor binding as measured by ^{3}H-lysergic acid diethylamide (^{3}H-LSD) in the blood platelets of depressed patients. Life Sci., 1989, 44, 725–734.
4. Barrett J.E., Vanover K.E.: 5-HT receptors as targets for the development of novel anxiolytic drugs: models, mechanisms and future directions. Psychopharmocology, 1993, 112, 1–12.
5. Barrett J.E., Witkin J.M., Mansbach R.S., Skolnick P., Weissman B.A.: Behavioural studies with anxiolytic drugs. III. Antipunishment actions of buspirone in pigeons do not involve benzodiazepine receptor mechanisms. J. Pharmacol. Exp. Ther., 1986, 238S, 1009––1013.
6. Beasley Ch.M., Masica D.N., Potvin J.H.: Fluoxetine: a review of receptor and functional effects and their clinical implications. Psychopharmocology, 1992, 107, 1–10.
7. Bel N., Artigas F.: Chronic treatment with fluvoxamine increases extracellular serotonin in frontal cortex but not in raphe nuclei. Synapse, 1993, 15, 243–245.
8. Blanchard R.J., Blanchard D.C.: Aggressive behaviour in the rat. Behav. Biol., 1977, 21, 197–224.
9. De Paulis T., Kumar Y., Johansson L., Ramsby L., Hall H., Sallemark M., Angeby-Moller K., Ögren S.-O.: Potential neuroleptic agents 4: chemistry, behavioral pharmacology, and inhibition of (3H)-spiperone binding of 3,5 disubstituted-((1-ethyl-2pyrroliolinyl)-methyl)-6-methoxy-salicylates. J. Med. Chem., 1986, 29, 61–69.
10. Detke M.J., Wieland S., Lucki I.: Blockade of the antidepressant-like effects of 8-OH-DPAT, buspirone and desipramine in the rat forced swim test by 5-HT_{1A} receptor antagonists. Psychopharmacology, 1995, 119, 47–54.
11. De Vry J., Glaser T., Schuurman T., Schreiber R., Traber J.: 5-HT_{1A} receptors in anxiety. In: New Concepts in Anxiety. Eds. Briley M., File S.E., MacMillan Press, London, 1991, 94–129.

12. De Vry J., Schreiber R., Glaser T., Traber J.: Behavioral pharmacology of 5-HT_{1A} agonists: animal models of anxiety and depression. In: Serotonin$_{1A}$ Receptors in Depression and Anxiety. Eds. Stahl S.M., Gastpar M., Keppel Hasselink J.M., Traber J., Raven Press, New York, 1992, 55–81.
13. Eison A.S., Temple D.L. Jr.: Buspirone: review of its pharmacology and current perspectives on its mechanism of action. Amer. J. Med., 1986, 80, 1–9.
14. Fabre L.F.: Buspirone in the management of major depression: a placebo-controlled comparison. J. Clin. Psychiat., 1990, 51, 55–61.
15. Fontenay W., Le Cornec J., Zaczyńska M., Debarle M.C., Simon P., Boissier J.-R.: Problèmes posés par l'utilisation de trois tests de comportement du rat pour l'étude des médicaments psychotropes. J. Pharmacol. (Paris), 1970, 1, 243–254.
16. Giral P., Martin P., Soubrie P., Simon P.: Reversal of helpless behavior in rats by putative 5-HT_{1A} agonists. Biol. Psychiat., 1988, 23, 237–242.
17. Gleeson S., Ahlers S.T., Mansbach R.S., Foust J.M., Barrett J.E.: Behavioral studies with anxiolytic drugs. VI. Effects on punished responding of drugs interacting with serotonin receptor subtypes. J. Pharmacol. Exp. Ther., 1989, 250, 809–817.
18. Goa K.L., Ward A.: Buspirone: a preliminary review of its pharmacological properties and therapeutic efficacy as an anxiolytic. Drugs, 1986, 32, 114–129.
19. Griffiths J., Shanks N., Anisman H.: Strain-specific alterations in comsumption of a palatable diet following repeated stressor exposure. Pharmacol. Biochem. Behav., 1992, 42, 219–227.
20. Handley S.L., Mc Blane J.W.: 5-HT drugs in animal models of anxiety. Psychopharmacology, 1993, 112, 13–20.
21. Katz R.J.: Animal model of depression: pharmacological sensitivity of a hedonic deficit. Pharmacol. Biochem. Behav., 1982, 16, 965–968.
22. Katz R.J., Roth K.A., Caroll B.J.: Acute and chronic stress effects on open field activity in the rat: implication for a model of depression. Neurosci. Biobehav. Rev., 1981, 5, 247–251.
23. Katz R.J., Sibel M.: Animal model of depression: tests of three structurally and pharmacologically novel antidepressant compounds. Pharmacol. Biochem. Behav., 1982, 16, 973–977.
24. Kendler K.S., Kessler R.C., Walters E.E., MacLean C., Neale M.C., Health A.C., Eaves L. J.: Stressful life events, genetic liability, and onset of major depression in women. Amer. J. Psychiat., 1995, 152, 833–842.
25. McKeith I.G., Marshall E.F., Ferrier I.N., Armstrong M.M., Kennedy W.N., Perry R.H., Perry E.K., Eccleston D.: 5-HT receptor binding in post-mortem brain from patiens with affective disorder. J. Affect. Disorders, 1987, 13, 67–74.
26. McMillen B.A., Matthews R.T., Sanghera M.K., Shepard P.D., German D.C.: Dopamine receptor antagonism by the novel antianxiety drug, buspirone. J. Neurosci., 1983, 3, 733–738.
27. Muscat R., Papp M., Willner P.: Reversal of stress-induced anhedonia by the atypical antidepressants, fluoxetine and maprotiline. Psychopharmacology, 1992, 433–438.
28. Nankai M., Yamada S., Muneoka K., Toru M.: Increased 5-HT_2 receptor-mediated behavior 11 days after shock in learned helplessness rats. Eur. J. Pharmacol., 1995, 281, 123–130.
29. Ossowska G., Klenk-Majewska B., Łupina T.: The effect of calcium channel antagonists on the aggressive behavior in chronically stressed rats. Pol. J. Pharmacol., 1994, 46, 403–408.
30. Pandey G.N., Pandey S.C., Janicak P.G., Marks R.C., Davis J.M.: Platelet serotonin-2 receptor binding sites in depression and suicide. Biol. Psychiat., 1990, 28, 215–222.
31. Pich E.M., Samanin R.: Disinhibitory effects of buspirone and low doses of sulpiride and haloperidol in two experimental anxiety models in rats: possible role of dopamine. Psychopharmacology, 1986, 89, 125–130.
32. Rickels K., Amsterdam J.D., Clary C., Puzzuoli G., Schweizer E.: Buspirone in major depression: a controlled study. J. Clin. Psychiat., 1991, 52, 34–38.
33. Robinson D.S., Rickels K., Feighner J., Fabre L.F., Gammans R.E., Shrotriya R.C., Alms D.R., Andary J.J., Messina M.E.: Clinical effects of the 5-HT_{1A} partial agonists in depression: a composite analysis of buspirone in the treatment of depression. J. Clin. Psychopharmacol., 1990, 10, 67S–76S.
34. Schweizer E., Rickels K.: Serotoninergic anxiolytics: a review of their clinical efficacy. In: 5-HT_{1A} Agonists, 5-HT_3 Antagonists and Benzodiazepines: Their Comparative Behavioural Pharmacology. Eds. Rodgers R.J., Cooper S.J., Wiley, Chichester, 1991, 365–376.
35. Sherman A.D., Sacquitne J.L., Petty F.: Specificity of the learned helplessness model of depression. Pharmacol. Biochem Behav., 1982, 16, 449–454.
36. Study R.E., Baker L.B.: Diazepam and (–)pentobarbital: fluctuation analysis reveals different mechanisms for potentiation of γ-aminobutyric acid responses in cultured central neurons. Proc. Nat. Acad. Sci. USA, 1981, 78, 7180–7184.
37. Tanda G., Frau R., Di Chiara G.: Local 5HT_3 receptors mediate fluoxetine but not desipramine-induced increase of extracellular dopamine in the prefrontal cortex. Psychopharmacology, 1995, 119, 15–19.
38. Taylor D.P., Moon S.L.: Buspirone and related compounds as alternative anxiolytics. Neuropeptides, 1991, 1, Suppl., 15–19.
39. Tedeschi D.H., Fowler P.J., Miller R.B., Macko E.: Pharmacological analysis of footshock-induced fighting behavior. In: Aggressive Behaviour. Eds. Garrattini S.S., Sigg K., Excerpta Medica, Amsterdam, 1969, 245–252.
40. Weissman B.A.: Interaction of buspirone with receptor binding sites. In: Buspirone: Mechanisms and Clinical Aspects. Eds. Tunnicliff G., Eison A.S., Taylor D.P., Academic Press, San Diego, 1991, 119–137.

41. Weissman B.A., Barrett J.E., Brady L.S., Witkin J.M., Mendelson W.B., Paul S.M., Skolnick P.: Behavioral and neurochemical studies on the anticonflict actions of buspirone. Drug Develop. Res., 1984, 4, 83–93.
42. Wieland S., Lucki I.: Antidepressant-like activity of 5-HT_{1A} agonists measured with the forced swim test. Psychopharmacology, 1990, 101, 497–504.
43. Willner P.: Animal models as simulations of depression. Trends Neurosci., 1991, 121, 131–136.
44. Willner P., Towell A., Sampson D., Sophokleous S., Muscat R.: Reduction of sucrose preference by chronic unpredictable mild stress and its restoration by a tricyclic antidepressant. Psychopharmacology, 1987, 93, 358–364.
45. Żebrowska-Łupina I., Ossowska G., Klenk-Majewska B.: Chronic stress reduced fighting behavior of rats: the effect of antidepressants. Pharmacol. Biochem. Behav., 1991, 39, 293–296.
46. Żebrowska-Łupina I., Ossowska G., Klenk-Majewska B.: The influence of antidepressants on aggressive behavior in chronically stressed rats: the role of dopamine. Pol. J. Pharmacol. Pharm., 1992, 44, 325–335.

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