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Effects of 8-OH-DPAT on Motor Activity in the Rat

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HILLEGAART, V., M.-L. WADENBERG AND S. AHLENIUS. *Effects of 8-OH-DPAT on motor activity in the rat.* PHARMACOL BIOCHEM BEHAV **32**(3) 797–800, 1989.—The administration of 8-OH-DPAT to rats produced a dose-dependent suppression of spontaneous locomotor activity in an open field arena. 8-OH-DPAT was administered in the dose range 12.5–1,600 $\mu g \cdot kg^{-1}$ SC. Vertical activity ("rearing") was more sensitive to the treatment than horizontal activity ("locomotion"), both in terms of potency and efficacy. The activity along the walls of the open field arena ("peripheral activity") was increased, and the rearing activity was decreased, relative to total horizontal activity and total activity, respectively. There were no effects by 8-OH-DPAT on treadmill locomotion. The rectal temperature was decreased by 8-OH-DPAT administration, not only in animals tested in the open field, but also in animals with an increased body temperature, produced by treadmill locomotion.

Open field Motor activity Treadmill 8-OH-DPAT 5-Hydroxytryptamine Rat

THE role of central 5-hydroxytryptamine (5-HT) in the regulation of motor mechanisms is complex. Thus, a depletion of brain and spinal 5-HT, as well as an increase in the availability of central 5-HT, can result in a decrease or an increase in motor activity depending on the experimental model used [see (9)]. The somata of 5-HT-containing neurons of the CNS are located in the lower brain stem and innervate the entire neuroaxis and forebrain via ascending and descending projections (7,25). Thus, there are numerous levels at which central 5-HT can affect motor behavior, from sensory perception, sensory-motor integration to motor effector mechanisms. As an example of the complexity encountered, it was recently shown that the local application of 5-HT into the dorsal raphe produced a decrease, and application into the median raphe produced an increase, in rat locomotor activity (12).

Central serotonergic mechanisms cannot only be subdivided according to localization of cell bodies and projections areas, but also according to receptor subtypes, possibly subserving distinct functions [see, e.g., (19)]. In addition to the general differentiation of 5-HT_1 and 5-HT_2 receptors, the 5-HT_1 receptor has been further subdivided 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} subtypes (15,18). 8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) has been identified as a 5-HT agonist (14) with preference for the 5-HT_{1A} binding site (17), and associated with particular functions (5, 8, 10, 20).

In the present experiments we have investigated the effects of systemically administered 8-OH-DPAT on motor activity in an open field, and on treadmill locomotion, in rats. In agreement with observations in mice (26), but in contrast to previous observations in rats (27), we found a dose-dependent suppression of spontaneous motor activity. Rectal temperature was also monitored in some of the animals observed in the open field and on the treadmill.

METHOD

Animals

Adult male Wistar rats, 250–350 g (ALAB, Laboratorietjänst AB, Sollentuna, Sweden), were used. The animals were housed under controlled conditions of temperature (20–21°C), humidity (55–65%), and light-dark cycle (12:12 hr, lights off at 06.00 hr), and arrived in the laboratory at least one week before being used in experiments.

Drugs

8-Hydroxy-2-(di-*n*-propylamino)tetralin·HBr (8-OH-DPAT) (RBI, Wayland, MA). 8-OH-DPAT was dissolved in 0.9% NaCl and injected subcutaneously in a volume of 2 $ml \cdot kg^{-1}$. Doses of 8-OH-DPAT were calculated on the salt. Controls received the saline vehicle.

Apparatus

The spontaneous motor activity was measured in photocell cages (700×700 mm). The photocells were sensitive to infrared light and observations were made in the dark. The apparatus allowed the registration of the following components: *Locomotor activity* (all horizontal activity as registered by a row of photocells, 40 mm above the floor of the cage), *Rearing* (vertical activity as registered by a second row of photocells, 125 mm above the floor), *Peripheral activity* (horizontal activity as registered by the first photocell in the bottom row, 40 mm from the wall). The relation of *peripheral* and *rearing* activities to *locomotor activity*

(all horizontal activity, including peripheral activity), and to *locomotor activity* plus *rearing*, respectively, were also calculated. Spontaneous motor activity observations started 10 min after 8-OH-DPAT administration, and the motor activity was recorded for 15 min. For further details see Ahlenius and Hillegaart (2).

Treadmill locomotion was observed on a rotating drum (o.d. 166 mm, 8 rpm), where the animals moved at a speed of 4 $m \cdot min^{-1}$. The animals were trained to walk on the drum for 2 consecutive days (2 sessions of 3 min per day). The third day, a pretest was performed and only those animals able to walk unaided for 3 min were included. Three out of 45 animals were excluded this way. In the experiments, treadmill locomotion was scored 0–5 depending on the time spent on the drum. A sqr transformation was used and maximal time was 3 min. For further details regarding test and scoring procedures see Ahlenius and Hillegaart (2).

Rectal temperature was measured by means of commercially available equipment (Model 2100, YSI, Yellow Springs, OH). Rectal temperature was measured in connection with spontaneous and treadmill motor activity experiments as described in the Results section and in legends to figures.

Statistics

Statistical analysis was performed by means of the appropriate parametric and nonparametric methods as described in figure legends and in the table.

RESULTS

Effects of 8-OH-DPAT on Spontaneous Motor Activity, Patterns of Activity and on Rectal Temperature

The locomotor activity and rearing activity were dose-dependently decreased by the administration of 8-OH-DPAT (Fig. 1, upper part). Rearing activity was affected already at the lowest dose of 8-OH-DPAT used, 12.5 $\mu g \cdot kg^{-1}$, whereas higher doses, 50–200 $\mu g \cdot kg^{-1}$, were needed to produce a reliable effect on locomotor activity. These differential effects by 8-OH-DPAT on spontaneous motor activity were particularly evident when calculating the corresponding ED_{50} values (the dose required to produce a 50% reduction of control activity as estimated by log-linear regression analysis): 3,500 $\mu g \cdot kg^{-1}$ (locomotion) and 12.5 $\mu g \cdot kg^{-1}$ (rearing). In fact, it can be questioned whether there is a clear dose-dependent suppression of locomotor activity.

There were also effects by 8-OH-DPAT on patterns of activity. Thus, there was a dose-dependent decrease in proportion rearing activity in relation to total activity. Furthermore, there were dose-related effects on the proportion peripheral activity to locomotor activity, indicating an increased wall activity up to 200 $\mu g \cdot kg^{-1}$, followed by a decrease in the proportion of this activity. Although there was an overall statistical effect on the peripheral activity relative to locomotion, the difference in activity between drug-treated and control animals did not reach statistical significance at any particular dose (Fig. 1, bottom part).

In agreement with previous reports in the literature, there was a decrease in the rectal temperature by 8-OH-DPAT administration (1, 10, 13) (Fig. 2). The decrease was dose-dependent and statistically significant at 100 $\mu g \cdot kg^{-1}$ and higher doses.

Effects of 8-OH-DPAT on Treadmill Locomotion and Interactions Between 8-OH-DPAT-Induced Effects on Treadmill Locomotion and on Rectal Termperature

There were no statistically significant effects by 8-OH-DPAT (400–1,600 $\mu g \cdot kg^{-1}$) on treadmill locomotion 20 min–2 hr after injection. The animals were visibly affected, however, with a dragging gait, but the motor coordination was apparently intact (Table 1).

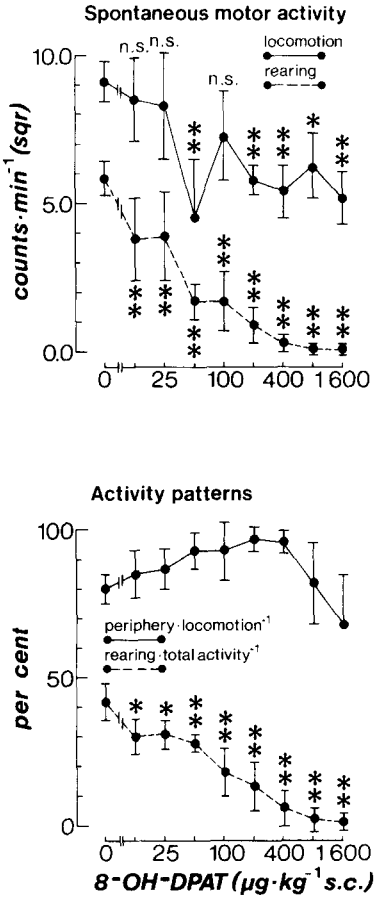

FIG. 1. Effects of 8-OH-DPAT on spontaneous locomotor activity and on activity patterns in the rat. The animals were given 8-OH-DPAT 0–1,600 $\mu g \cdot kg^{-1}$ SC, 10 min before a 15-min test session in the activity boxes. The results are presented as means ± S.D. based on observations of 5 animals per dose of 8-OH-DPAT. Statistical evaluation was performed by means of a one-way ANOVA, followed by the Dunnett's *t*-test for comparisons with saline-treated controls (28). *Locomotion:* $F(8,36) = 8.21$, $p<0.01$; *Rearing:* $F(8,36) = 29.46$, $p<0.01$; *Periphery·Locomotion*$^{-1}$: $F(8,36) = 4.92$, $p<0.01$; *Rearing·Total activity*$^{-1}$: $F(8,36) = 30.13$, $p<0.01$. $^{n.s.}p>0.05$; $^{*}p<0.05$; $^{**}p<0.01$.

The rectal temperature was increased in saline-treated controls and decreased in 8-OH-DPAT-treated (1,600 $\mu g \cdot kg^{-1}$) animals, in comparison with a control group not trained or tested on the treadmill (Fig. 3). In this experiment, rectal temperature was measured at this dose of 8-OH-DPAT only. As mentioned above, the 8-OH-DPAT-treated animals were not impaired on the treadmill and all animals thus walked for 3 min on the treadmill at each time interval.

DISCUSSION

The major finding of the present study was a decrease in spontaneous motor activity in rats after administration of 8-OH-DPAT. The effect was more pronounced on rearing activity than on locomotor activity. This is also clear from the calculation of the ratio between rearing and locomotor activity as seen at the bottom of Fig. 1. Rearing is generally taken as an index of

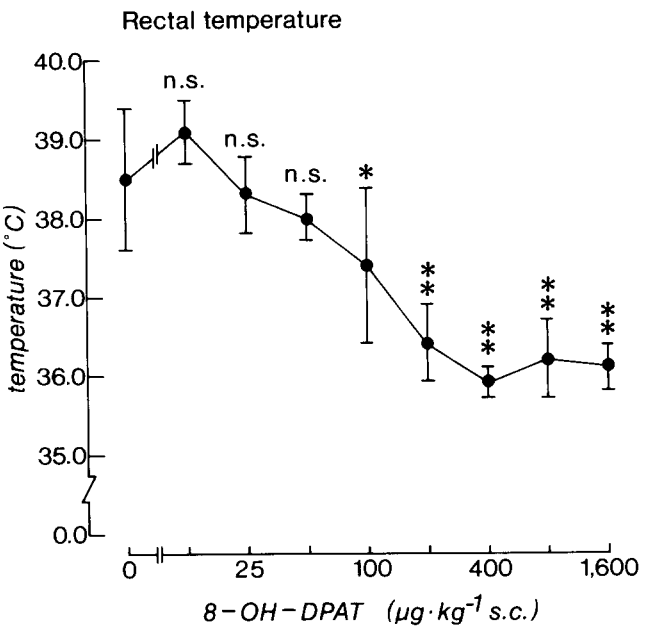

FIG. 2. Effects of 8-OH-DPAT on rectal temperature in the rat. Rectal temperature measurements were made immediately upon completion of the activity tests as presented in Fig. 1. The temperature is presented as means ± S.D., and statistical evaluation was performed by means of one-way ANOVA followed by the Dunnett's *t*-test for comparisons with saline-treated controls (28). $F(8,36)=21.23$, $p<0.01$. $^{n.s.}p>0.05$, $^{*}p<0.05$; $^{**}p<0.01$.

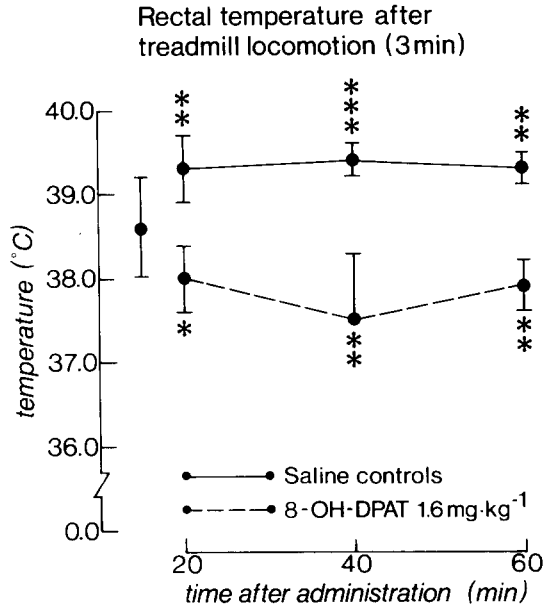

FIG. 3. Effects of treadmill locomotion on rectal temperature in saline- and 8-OH-DPAT-treated rats. The rectal temperature was measured immediately after the treadmill tests at the time intervals indicated in Table 1. The results are presented as means ± S.D. and statistical evaluation was performed by means of a *t*-test for comparisons with a separate group of saline-treated controls (n = 9), not tested on the treadmill.

exploratory activity, and 8-OH-DPAT thus displays some selectivity for this behavior. It should be noted that a centrally active DA agonist, like apomorphine, could produce a similar pattern of stereotyped forward locomotion (at the expense of rearing activity) [e.g., (16,24)]. Such an effect would also show up as a loss of habituation of activity over the 15 min in the open field (measured every 3 min). Comparison of the habituation in controls and in animals treated with the different doses of 8-OH-DPAT indicated a statistically significant interaction between treatment and time, at the 50 μg dose, due to faster habituation, $F(4,32)=2.97$, $p<0.05$, and at the 200 μg dose, due to slower habituation, $F(4,32)=3.65$, $p<0.05$. Otherwise, there were no statistically significant differences between the habituation in controls and in drug-treated animals (data not shown), and the marked decrease in rearing activity, produced by 8-OH-DPAT, is probably not due to stereotyped forward locomotion.

TABLE 1

TIME- AND DOSE-EFFECT RELATIONSHIPS OF 8-OH-DPAT ON TREADMILL LOCOMOTION

8-OH-DPAT	Time After Administration (min)			
(μg·kg^{-1})	20	40	60	120
0	4.9	5.0	5.0	5.0
400	5.0	4.9	4.9	5.0
800	4.9	5.0	5.0	5.0
1,600	4.7	4.9	5.0	5.0

Treadmill performance was scored (0–5), as described in the Method section. The table shows median values based on observations of 10 animals per dose. Statistical evaluation by means of Kruskal-Wallis 2-way ANOVA (21) indicated no statistically significant effects at any time interval.

In contrast to suppression of spontaneous motor activity in the present study, Tricklebank *et al.* (27) have shown an increase in ambulation by 8-OH-DPAT administration. At least 3 factors may account for this apparent discrepancy. Firstly,their use of juvenile, rather than adult, rats. Secondly, the employment of a brief, 5 min, habituation period, and finally, possibly related to these differences, much higher doses of 8-OH-DPAT were required to produce stimulation of ambulation than the doses required to suppress exploratory behavior. It should be noted, however, that we did not observe a stimulation of spontaneous motor activity in doses up to 1,600 μg·kg^{-1}. The recent demonstration that the suppression of locomotor activity and rearing produced by 8-OH-DPAT can be antagonized by (−)pindolol pretreatment suggests that this suppression of motor activity by 8-OH-DPAT is mediated by 5-HT_{1A} receptors (Johansson and Ahlenius, submitted).

The administration of 8-OH-DPAT produces various signs of the "5-HT syndrome," including hindlimb abduction, flattened body posture and forepaw treading (14, 23, 27). Although much higher doses of 8-OH-DPAT than those employed in the present experiments are needed to produce a full blown "5-HT syndrome," it cannot be excluded that even small effects in this direction could influence measurements of open field motor activity. It should be noted, however, that not even the highest doses (400–1,600 μg·kg^{-1}) used in the present experiments affected treadmill locomotion, indicating that locomotor coordination was unimpaired. For comparison, it can be mentioned that a low dose of haloperidol, 0.16 mg·kg^{-1}, not causing any other visible extrapyramidal motor effects, disrupts the treadmill performance (2).

The decrease in rectal temperature produced by 8-OH-DPAT is

in good agreement with data reported in the literature [see (11)]. Furthermore, motor activity and rectal temperature appeared to be affected in the same dose range. Interestingly, the decrease in body temperature was still evident in animals with an elevated body temperature due to treadmill locomotion.

8-OH-DPAT is generally considered to be a 5-HT_{1A} agonist and/or a partial 5-HT agonist (4,17), and this may be the mechanism whereby 8-OH-DPAT affects motor activity and body temperature regulation. It should also be mentioned, however, that 8-OH-DPAT selectively inhibits DA synthesis in limbic ventral and medial areas of the rat striatum, as studied by DOPA accumulation after decarboxylase inhibition in reserpine-treated animals (3). Such effects, although not statistically significant until around 200 $\mu g \cdot kg^{-1}$ and higher doses of 8-OH-DPAT, could be responsible or contribute to the effects observed in the present experiments. It should be noted that 8-OH-DPAT-induced changes on prolactin secretion have been suggested to be partially due to stimulation of DA receptors (6,22), although other explanations can not be ruled out.

In conclusion, administration of 8-OH-DPAT produced a dose-dependent decrease in rearing activity and a not clearly dose-dependent suppression of forward locomotion. The suppression of motor activity by 8-OH-DPAT is probably not related to effects on motor coordination since treadmill locomotion was unaffected by 8-OH-DPAT in the dose range affecting motor activity in the open field.

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REFERENCES

1. Ahlenius, S.; Criborn, C.-O.; Henriksson, C. Central 5-HT and the respiratory response to acoustic stimulation in awake rats: Effects of PCPA, 5-HTP and 8-OH-DPAT. J. Neural Transm. 63:285–295; 1985.
2. Ahlenius, S.; Hillegaart, V. Involvement of extrapyramidal motor mechanisms in the suppression of locomotor activity by antipsychotic drugs: A comparison between the effects produced by pre- and post-synaptic inhibition of dopaminergic neurotransmission. Pharmacol. Biochem. Behav. 24:1409–1415; 1986.
3. Ahlenius, S.; Hillegaart, V.; Wijkstrom, A. Region-selective effects by 8-OH-DPAT on rat brain dopamine synthesis in vivo. Neurochem. Int. 13(Suppl. 1):80; 1988.
4. Ahlenius, S.; Larsson, K. Antagonism by lisuride and 8-OH-DPAT of 5-HTP-induced prolongation of performance of male rat sexual behavior. Eur. J. Pharmacol. 110:379–381; 1985.
5. Ahlenius, S.; Larsson, K.; Svensson, L.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Wikstrom, H.; Sanchez, D.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G. Effects of a new type of 5-HT receptor agonist on male rat sexual behavior. Pharmacol. Biochem. Behav. 15:785–792; 1981.
6. Carlsson, M.; Eriksson, E. A central serotonin receptor agonist, 8-hydroxy-2-(di-n-propylamino)tetralin, has different effects on prolactin secretion in male and female rats. Acta Pharmacol. Toxicol. 58:297–302; 1986.
7. Dahlstrom, A.; Fuxe, K. Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in cell bodies of brain neurons. Acta Physiol. Scand. [Suppl.] 232:1–55; 1964.
8. Dourish, C. T.; Hutson, P. H.; Curzon, G. Low doses of the putative serotonin agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) elicit feeding in the rat. Psychopharmacology (Berlin) 86:197–204; 1985.
9. Gerson, S. C.; Baldessarini, R. J. Motor effects of serotonin in the central nervous system. Life Sci. 27:1435–1451; 1980.
10. Goodwin, G. M.; Green, A. R. A behavioural and biochemical study in mice and rats of putative agonists and antagonists for 5-HT_1 and 5-HT_2 receptors. Br. J. Pharmacol. 84:743–753; 1985.
11. Green, A. R.; Goodwin, G. M. The pharmacology of the hypothermic response of rodents to 8-OH-DPAT administration and the effects of psychotropic drug administration on this response. In: Dourish, C. T.; Ahlenius, S.; Hutson, P. H., eds. Brain 5-HT_{1A} receptors. Chichester: Ellis Horwood; 1987:161–176.
12. Hillegaart, V.; Ahlenius, S.; Larsson, K. Different roles of the median and dorsal raphe nuclei in rat serotonergic motor functions. Neurochem. Int. 13(Suppl. 1):126; 1988.
13. Hjorth, S. Hypothermia in the rat induced by the potent serotoninergic agent 8-OH-DPAT. J. Neural Transm. 61:131–135; 1985.
14. Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G. 8-Hydroxy-2-(di-n-propylamino)tetralin, 8-OH-DPAT, a potent and selective simplified ergot congener with central 5-HT-receptor stimulating activity. J. Neural Transm. 55:169–188; 1982.
15. Hoyer, D.; Engel, G.; Kalkman, H. O. Molecular pharmacology of 5-HT_1 and 5-HT_2 recognition sites in rat and pig brain membranes: radioligand binding studies with [^{3}H]5-HT, [^{3}H]8-OH-DPAT, (−) [^{125}I]iodocyanopindolol, [^{3}H] mesulergine and [^{3}H]ketanserin. Eur. J. Pharmacol. 118:13–23; 1985.
16. Klint, T.; Hillegaart, V.; Edlund, P. O.; Wijkstrom, A.; Ahlenius, S. Effects of postpuberal castration on dopamine receptor sensitivity in the male rat brain. Pharmacol. Toxicol. 62:64–68; 1988.
17. Middlemiss, D. N.; Fozard, J. R. 8-Hydroxy-2-(di-n-propylamino)tetralin discriminates between subtypes of the 5-HT_1 recognition site. Eur. J. Pharmacol. 30:151–153; 1983.
18. Pazos, A.; Palacios, J. M. Quantitative autoradiographic mapping of serotonin receptors in rat brain. I. Serotonin-1 receptors. Brain Res. 346:205–230; 1985.
19. Peroutka, S. J.; Snyder, S. H. Two distinct serotonin receptors: regional variations in receptor binding in mammalian brain. Brain Res. 208:339–347; 1981.
20. Renyi, L. The involvement of 5-HT_1 and 5-HT_2 receptors in different components of the 5-HT syndrome in the rat. Neuroscience S22:225P; 1987.
21. Siegel, S. Nonparametric statistics for the behavioral sciences. New York: McGraw-Hill; 1956.
22. Simonovic, M.; Gudelsky,G. A.; Meltzer, H. Y. Effect of 8-hydroxy-2-(di-n-propylamino)tetralin on rat prolactin secretion. J. Neural Transm. 59:143–149; 1984.
23. Smith, L. M.; Peroutka, S. J. Differential effects of 5-hydroxytryptamine$_{1A}$ selective drugs on the 5-HT behavioral syndrome. Pharmacol. Biochem. Behav. 24:1513–1519; 1986.
24. Stahle, L.; Ungerstedt, U. Different behavioural patterns induced by the dopamine agonist apomorphine analysed by multivariate statistics. Pharmacol. Biochem. Behav. 24:291–298; 1986.
25. Steinbusch, H. W. M.; Nieuwenhys, R. The raphe nuclei of the rat brainstem: A cytoarchitectonic and immunohistochemical study. In: Emson, P. C., ed. Chemical neuroanatomy. New York: Raven Press; 1983:131–207.
26. Svensson, K.; Larsson, K.; Ahlenius, S.; Arvidsson, L.-E.; Carlsson, A. Evidence for a facilitatory role of central 5-HT in male mouse sexual behavior. In: Dourish, C. T.; Ahlenius, S.; Hutson, P. H., eds. Brain 5-HT_{1A} receptors. Chichester: Ellis Horwood; 1987:199–210.
27. Tricklebank, M. D.; Forler, C.; Fozard, J. R. The involvement of subtypes of the 5-HT_1 receptor and of catecholaminergic systems in the behavioural response to 8-hydroxy-2-(di-n-propylamino)tetralin in the rat. Eur. J. Pharmacol. 106:271–282; 1984.
28. Winer, B. J. Statistical principles in experimental design. New York: McGraw-Hill; 1971.