Dopaminergic Agonists and Muscarinic Antagonists Improve Lateralization in Hemiparkinsonian Rats in a Novel Exploratory Y-maze

Makoto Nakagawa, Makoto Ohgoh, Yukio Nishizawa and Hiroo Ogura

Tsukuba Research Laboratories, Eisai Co., Ltd., 5-1-3 Tokodai, Tsukuba-shi, Ibaraki 300-2635, Japan
Running title: Anti-Parkinsonian Drugs Improve Bias in Exploratory Y-maze

Correspondence should be addressed to Makoto Nakagawa, Ph.D., Tsukuba Research Laboratories, Eisai Co., Ltd., 5-1-3 Tokodai, Tsukuba-shi, Ibaraki 300-2635, Japan
Phone: +81-29-847-5694 Fax: +81-29-847-2037 E-mail: m-nakagawa@hhc.eisai.co.jp

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Abbreviations: PD, Parkinson’s disease; NMDA, N-methyl-D-aspartate; 6-OHDA, 6-hydroxydopamine; MFB, medial forebrain bundle; NMS, N-methylscopolamine

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Abstract

Parkinson’s disease (PD) is characterized by the degeneration of nigrostriatal dopaminergic neurons. Its primary clinical symptoms are akinesia, tremor and rigidity, which usually start from one side, resembling the lateralization in hemiparkinsonian rats having 6-hydroxydopamine-induced unilateral lesion of the medial forebrain bundle. A novel exploratory Y-maze was designed to detect the lateralization of hemiparkinsonian rats in terms of biased turns in the maze. Dopamine agonists, levodopa (L-3,4-dihydroxyphenylalanine, 10-30 mg/kg) and apomorphine (0.1-0.3 mg/kg), but not methamphetamine (0.5 - 2 mg/kg), improved the lateralization in the rat model. However, high doses of the dopamine agonists, 30 mg/kg and 0.3 mg/kg, respectively, caused small movements in the arms that appeared to parallel the increase in counts/turn in the Y-maze. Interestingly, the muscarinic antagonists trihexyphenidyl and scopolamine improved lateralization moderately, while increasing total turns, an index of locomotive activity. MK801 (0.3 mg/kg), an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, increased total counts, but did not alleviate the lateralization. The α2-adrenoceptor antagonist idazoxan (1, 10 mg/kg) and NBQX (1 and 3 mg/kg), a non-NMDA glutamate receptor antagonist, did not affect any of the indices. These findings suggest that the clinical action of drugs on unbalanced movement in PD could be predicted by measuring their effects on lateralization of the 6-hydroxydopamine-lesioned rat model in this exploratory Y-maze.
Parkinson’s disease (PD) is a progressive neurological disorder affecting mainly elderly people. In this disease, the degeneration of nigrostriatal dopaminergic neurons is evident, as revealed by direct biochemical assay (Hornykiewicz, 1966; Hornykiewicz, 1998) and more recently by positron emission tomography, measuring the uptake of the dopamine precursor $^{18}$F-DOPA (Brooks et al., 1990, Takikawa et al., 1994). A deficit in this dopaminergic input into the striatum causes overactivity in the indirect motor pathway accompanied with underactivity in the direct motor pathway in the basal ganglia (Wichmann and DeLong 1993). The imbalance of these motor circuits leads to motor dysfunction, including akinesia (impaired initiation of movement) and bradykinesia (reduced amplitude and velocity of voluntary movement), which produce the characteristic features of PD (Kish et al., 1988).

The immediate metabolic precursor of dopamine, levodopa (L-3,4-dihydroxyphenylalanine, L-dopa), has been employed in medications for the treatment of PD. It provides a drastic reversal of all signs and symptoms of PD except dementia and postural instability (Williams and Carlyle, 1979, Silver and Ruggieri, 1998). Historically, direct dopamine agonists, such as bromocriptine and pergolide, have also been used as adjuncts to levodopa in patients with advanced disease who already have motor complications (Olanow et al., 2001). However, it has recently been demonstrated that initiation of therapy with a direct dopamine agonist is associated with a reduced risk for development of motor complications to levodopa (Poewe, 1998; Watts, 1997). Until levodopa was introduced, muscarinic antagonists had been the most effective class of drugs for treatment of PD (Dalvi and Ford, 1998, Kopin, 1993), but they are now prescribed in a supportive role in the treatment of the disorder (Standaert...
and Young, 1995).

Because 6-hydroxydopamine (6-OHDA) is able to produce selective dopaminergic lesions, it has been used extensively in rodents to reproduce PD symptoms (Ungerstedt and Arbuthnott, 1970; Schwarting and Huston, 1996). After unilateral lesioning with 6-OHDA at dopaminergic somata or ascending dopaminergic fibers, dopaminergic agents drastically enhance turning. Direct dopamine agonists such as apomorphine act on upregulated dopamine receptors and elicit contralateral turning, while indirect dopaminergic stimulants such as methamphetamine increase ipsilateral turning (Ungerstedt and Arbuthnott, 1970, Gerlach and Riederer, 1996, Schwarting and Huston, 1996). The potency of dopaminergic agents can be easily quantified in terms of this turning behavior of unilaterally lesioned rats. Because drug-induced turning occurs as a result of dopaminergic receptor supersensitivity, it is difficult to observe behavioral/motor deficits due to dopamine depletion within the striatum in the absence of challenge with dopaminergic agents, and therefore this method cannot be used for the pharmacological evaluation of non-dopaminergic agents. Moreover, the relation of the drug-induced turning to the clinical symptoms of PD is unclear.

Animals with a unilateral dopaminergic lesion must have some impairment of contralateral motor function, which might correspond to clinical PD symptoms, such as akinesia and bradykinesia. If we can evaluate the degree of the motor dysfunction and assess the degree to which a drug can improve it, we may be able to understand better how drugs work clinically to improve akinesia and bradykinesia. Recently, a new evaluation method, the so-called stepping test (Olsson, et al., 1995, Kirik, et al., 1998, Mukhida, et al., 2001), has been proposed. Although this method can assess akinesia or
rigidity of PD model rats very sensitively, the successful use of such a model depends on the investigator’s technique. In this study, we have developed a novel method named the exploratory Y-maze, with which the lateralization of hemiparkinsonian rats can be easily assessed in terms of biased selection of arms in the maze. We have used this model to examine various anti-parkinsonian drugs and compounds, in order to see if they improve the lateralization in unilaterally 6-OHDA-lesioned rats. We found, interestingly, that not only dopaminergic agonists, but also muscarinic antagonists alleviated the bias of these rats.
Methods

Animals

Male Wistar rats (5 weeks old, weighing 130-150 g, Charles River Japan, Inc., Kanagawa, Japan) were used. Prior to the study, rats were acclimatized to quarters maintained at a room temperature of 23 ± 1 °C with 55 ± 5% relative humidity under a 12 hour light/dark cycle for 1 week. During periods of acclimatization and for 4 weeks after operation, solid diet (FM, Oriental Yeast Industry, Tokyo, Japan) and water were provided ad libitum. During experiments, the solid diet was limited to 20 g/animal /day for body weight control (300-400 g).

Surgical procedure for medial forebrain bundle lesion

Animals were anesthetized with pentobarbital (Nembutal®, Abbott Laboratories, Ill, USA)(50 mg/kg i.p.) and placed in rat stereotaxic apparatus with the incisor bar fixed at - 2.0 mm. Each animal received a unilateral injection of 4 µl of 6-OHDA HCl (Sigma Co., St Louis, MO, USA)(4 mg/ml in 0.1% ascorbic acid) into the right medial forebrain bundle (MFB) through a stainless steel cannula at a rate of 0.4 µl/min using a microliter syringe pump. The stereotaxic coordinates, based on Paxinos and Watson (1996), were 2.5 mm posterior from the bregma, 1.8 mm lateral to the midline and 7.8 mm from the dura. The cannula was left for 5 minutes after the end of the injection to prevent backward flow and to allow for toxin diffusion. Thirty minutes before and immediately after operation, rats were injected i.p. with 25 mg/kg desipramine to prevent concurrent damage to noradrenergic pathways by 6-OHDA infusion (Roberts et al., 1975).
Lateralization in the exploratory Y-maze.

Lateralization, a locomotor bias, was measured in an exploratory Y-maze made of white acrylic boards, as shown in Fig. 1. The exploratory Y-maze was placed in a dark room. Each arm was 30 cm long, 11 cm wide and 12 cm high, and was equipped with a photoelectric switch (type E3S-BT11, Omron Co., Tokyo, Japan) (4 cm above the floor, 18 cm from the tip). At the center of the maze, the space was narrowed and the ceiling was lowered. Rats could go only in the direction of their nose at the center, while the space in each arm was large enough for them to turn there. Interruptions of the infrared beams were recorded through a digital I/O interface (Muromachi Kikai Co., Ltd. Tokyo, Japan) at 0.1 second intervals by a computer (PC9801FA or PC9801RX, NEC Tokyo, Japan) outside the testing room. The ratio of choice of the right arm (right%) was measured for 30 min as an index of lateralization. Otherwise, the number of interruptions of the beam (total count), the number of entrances from one arm to another (total turns) and number of counts per turn (counts/turn) were recorded. Total counts reflects small movements within one arm, while total turns reflect major movement to another arm. However, both indexes reflect the spontaneous motor activity of the animals. One more index, the counts/turn, reflects the quality of the movement. This index indicates the ratio of large and small movements.

Lesion verification

Four weeks after the operation, rats were placed in the exploratory Y-maze and locomotor bias was measured. The criteria for a successful lesion and the inclusion of
the animal in subsequent drug studies were set as more than 85% average right% and more than 80% right% in each of two consecutive measurements.

Drug treatment

Apomorphine (Sigma Chemical Co., St Louis, MO, USA) dissolved in 0.1% ascorbic acid and NBQX (Tocris Cookson Inc., Ballwin, MO, USA) dissolved in saline made slightly alkaline with 0.1 N NaOH were administered immediately before recording of movements in the exploratory Y-maze. Methamphetamine (Dainippon Pharmaceutical Co. Ltd., Osaka, Japan), MK801 (Sigma Chemical Co., St Louis, MO, USA), scopolamine (Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan) and N-methylscopolamine (Sigma Chemical Co., St Louis, MO, USA) were each dissolved in saline. Idazoxan (Sigma Chemical Co., St Louis, MO, USA) was suspended in 0.5% methylcellulose. Agents were administered intraperitoneally 15 minutes before recording of movements in the exploratory Y-maze. Levodopa and benserazide (Sigma Chemical Co., St Louis, MO, USA) (4:1) were suspended in 0.5% methylcellulose and then administered intraperitoneally 15 and 45 minutes before recording, respectively.

Biochemical analysis

At the end of the experiments, rats were decapitated and the brain was removed. The whole striata and frontal cortex were dissected rapidly on ice and immediately frozen in liquid nitrogen until analysis. Determination of the dopamine and norepinephrine contents was performed as described previously (Kagaya et al., 1996). 3,4-Dihydroxybenzylamine was used as an internal standard. Monoamine levels were
analyzed on a 150-mm ODS column (CA-5 ODS, Eicom, Kyoto, Japan) combined with an ECD detector (ECD-100, Eicom) and the assay was conducted by the internal standard method.

Statistical analysis

Behavioral data were analyzed by means of one-way ANOVA followed by Dunnett’s test, or by means of the F test followed by Student’s t test using the software package SAS 6.12 (SAS Institute Japan, Tokyo, Japan). In all tests, differences were considered significant when p was smaller than 0.05.
Results

Effect of medial forebrain bundle (MFB) lesion

The effect of MFB lesion was assessed, using the 4 indices described in Methods, 4 weeks after lesioning. The value of right% in the naive group was almost at the chance level. As shown in Fig. 2, right% was significantly increased to about 80% in lesioned animals (t = 11.93, p < 0.0001), whereas other indices, total counts and total turns, showed no change. The increase of right% was highly reproducible, and did not change during repeated trials.

The relationship between right% and dopamine content in the striatum or norepinephrine content in the frontal cortex was examined. When animals showed a right% value of more than 80%, the dopamine content in the striatum was always less than 10% (Fig. 3 upper panel). When the striatal dopamine content remained above 10%, it appeared to correlate negatively with right% values. In some cases, however, severe depletion of striatal dopamine did not cause lateralization of more than 80%, although almost all such animals showed higher right% values than the chance level (50%). On the other hand, animals having right% values of more than 85% showed various norepinephrine levels. Thus, norepinephrine content did not correlate straightforwardly with right% values, in contrast to dopamine content. The values of the correlation coefficient between striatum DA% and right% and between cortex NE% and right% were 0.68 and 0.19, respectively.

Effect of dopaminergic drugs

Intraperitoneal administration of the dopamine precursor levodopa with benserazide
significantly reduced right% at 10 mg/kg (t = 2.52, p = 0.045) without significant changes of total counts, total turns and counts/turn. At a higher dose, 30 mg/kg, right% was also reduced (t = 2.51, p = 0.045), while total turns was drastically decreased (t = 2.78, p = 0.024) and total counts was increased (t = 2.73, p = 0.027) (Fig. 4, upper panel). As a result, counts/turn at 30 mg/kg was markedly increased (t = 4.62, p = 0.0001). At this dose, we observed that the animals turned counterclockwise in their home cage before and after the measurement in the Y-maze.

A short-acting dopamine agonist, apomorphine, was injected subcutaneously. As shown in Fig. 4, right% was significantly reduced at 0.1 mg/kg (t = 2.80, p = 0.022), again without significant changes in total counts, total turns and counts/turn. At a higher dose of 0.3 mg/kg, right% was reduced (t = 5.20, p = 0.00002), while total turns tended to be decreased (t = 2.06, p = 0.125) and the total counts value was increased (t = 3.44, p = 0.004). As with levodopa, counts/turn was significantly increased at this dose (t = 5.07, p = 0.00003).

On the other hand, an indirect dopamine agonist, methamphetamine, did not affect right%, while it significantly increased total counts and total turns at 0.5 mg/kg (t = 3.16, 3.01, p = 0.0067, 0.0097 respectively) (Fig. 4).

Effects of anticholinergic drugs

Trihexyphenidyl, an anticholinergic drugs commonly prescribed for treatment of early phase PD (Olanow et al., 2001), was tested (Fig. 5). Interestingly, 10 mg/kg of trihexyphenidyl significantly decreased right% (t = 2.70, p = 0.019), although it increased both counts and turns at the same dose (t = 3.14, 4.55, p = 0.006, 0.00009
respectively). In marked contrast to dopaminergic drugs, trihexyphenidyl increased total turns and consequently counts/turn decreased at the same dose ($t = 4.23, p = 0.00025$).

In order to examine whether this effect was related to the central nervous system, we compared the effect of scopolamine, which can enter the brain, with that of N-methylscopolamine, which hardly passes though the blood brain barrier. Scopolamine showed almost the same effect as trihexyphenidyl, while N-methylscopolamine had only a small effect on total counts (Fig. 5).

Effects of other drugs under consideration for therapeutic use in PD

We tested the non-NMDA antagonist NBQX, the NMDA antagonist MK801 and the $\alpha_2$ antagonist idazoxan. Among these drugs, only MK801 at 0.3 mg/kg significantly increased total counts ($t = 2.87, p = 0.017$) and total turns ($t = 2.94, p = 0.015$). However, this compound did not improve lateralization at all. Idazoxan and NBQX did not significantly change any of the indices at 1 or 10 mg/kg, and at 1 or 3 mg/kg, respectively (Fig. 6).
Discussion

In PD patients, 70-80% of striatal dopamine content and 50% of dopaminergic neurons have been already lost when symptoms appear (Dunnett and Björklund, 1999). The symptoms are asymmetric, with one side more affected than the other. A comparison of $[^{123}\text{I}]\beta$-CIT binding in the striatum contralaterally and ipsilaterally to the affected body side in patients with hemiparkinsonism revealed a significant difference (Brücke et al., 1997), suggesting that a bias of dopaminergic degeneration causes hemiparkinsonism. When dopaminergic neurons in experimental animals are damaged unilaterally with 6-OHDA, the animals also show a movement bias. Measurement of turning behavior has been the most frequent approach to quantitate the bias and to assess the effects of dopaminergic drugs. In this study, we could clearly and quantitatively detect the locomotor bias (lateralization) in unilaterally 6-OHDA-lesioned rats by using a newly developed exploratory Y-maze method, in the absence of any drug. Furthermore, muscarinic antagonists, trihexyphenidyl and scopolamine, improved the lateralization in this rat PD model, like the dopamine agonists levodopa and apomorphine.

In our study, when unilaterally MFB-lesioned rats showed lateralization, the dopamine content in the striatum was always less than 10% of that in the non-lesioned side. This is very similar to the clinical findings in PD, as described above. However, we found that dopamine depletion did not cause lateralization in some cases. Rats that were completely depleted of dopamine and norepinephrine did not always show complete lateralization, although norepinephrine was still found to be present in the frontal cortex of animals that showed right% values of over 85% in the maze (Fig. 3).
is difficult to explain this finding, but one possibility is that the lesion causing complete
depletion of dopamine and norepinephrine may have been too severe, damaging other
surrounding neurons. Such damage to other neuronal circuits might differently affect
lateralization in such cases.

Dopaminergic drugs improve PD symptoms, although their side effects, such as
dyskinesia, require caution in clinical use. Levodopa and apomorphine reduced the
right% value of hemiparkinsonian rats, suggesting that dopaminergic drugs are
effective to ameliorate the motor imbalance caused by unilateral dopaminergic
lesioning. High dosages of these drugs increase counts, decrease turns and result in an
increase in counts/turn (Figs. 4, 5). Before and after we recorded lateralization in the
Y-maze, counterclockwise turning of rats treated with a high dose of levodopa was
frequently observed in the home cage. This observation suggests that high doses of
dopamine agonists decrease large movements and increase small movements
simultaneously. In 6-OHDA-lesioned rats, postsynaptic dopamine receptors on the
lesioned side are supersensitive, so that levodopa and apomorphine act on the lesioned
side more efficiently than on the normal side, and lateralization is improved. When a
high dose of dopamine agonists is applied, dopamine receptors are excessively
activated, in particular in the lesioned side, and so this behavior is observed, in addition
to amelioration of bias. Although measurement of turning behavior can easily be used
to quantify the potency of dopaminergic drugs, turning is increased in a manner that
depends on the dose of dopamine agonist, which is not the case with our Y-maze. A
major advantage of our system is that we can assess movement both qualitatively and
quantitatively under each experimental condition. Regarding the significance of an
increase of counts/turn, this index may reflect certain forms of dyskinesia observed in the clinical situation. Marsden et al. reported that, at least during the initial period of treatment, levodopa-induced dyskinesias occurred at the same time as the greatest degree of clinical improvement, and were predominantly choreic in nature (1981). We think that the phenomena seen with high doses of levodopa and apomorphine may reflect such clinical symptoms seen when the effect of the drug is most apparent.

Indirect dopamine agonists, such as methamphetamine, did not improve lateralization, but increased locomotion. Methamphetamine increased total counts and total turns without changing counts/turn. Because nerve terminals of dopamine neurons on the lesioned side in the striatum of hemiparkinsonian rats were already lost, methamphetamine could not enhance the release of dopamine on the lesioned side, though it did so on the normal side.

Interestingly, anticholinergics improved lateralization of hemiparkinsonian rats (Fig. 7). Anticholinergics are typically used in younger PD patients (i.e., 70 years of age or less), in whom tremor is a dominant clinical feature and cognitive function is preserved (Olanow & Koller, 1998). Because N-methylscopolamine does not pass through the blood-brain barrier and did not affect the right% value, the effects are likely to be mediated through the central cholinergic system. It has been reported that muscarinic antagonists potentiated rotation induced by a D1 agonist (Morelli et al., 1993) and also that muscarinic agonists act functionally like dopamine antagonists (Fink-Jensen et al., 1998), so muscarinic antagonists may act functionally like dopamine agonists and improve lateralization. Domino and Lisong (1998) reported that trihexyphenidyl enhanced contraversive turning in
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced hemiparkinsonian monkeys. Muscarinic antagonists were also able to antagonize reserpine-induced rigidity in rats (Goldstein et al., 1975). Furthermore, anticholinergics were able to alleviate akinesia and movement initiation deficits in the 6-OHDA-lesioned rat model (Schallert, et al., 1978, Schallert, et al., 1979). These results are consistent with our finding that anticholinergics work in a PD model. In the case of anticholinergics, counts/turn was decreased at high dosage, which is opposite to the observation with a dopaminergic agonist. While a high dosage of scopolamine improved lateralization, scopolamine at the same dosage is also known to induce amnesia (Bammer, 1982, Ogura et al., 2000). Although scopolamine improved lateralization in this study, this effect may not be useful in the clinical situation, because of the other effects of anticholinergics (Molchan et al., 1992), such as eliciting amnesia.

AMPA, NMDA or α2-adrenergic antagonists do not improve the lateralization in unilaterally lesioned rats. A non-competitive AMPA antagonist was reported to improve levodopa-induced dyskinesia in MPTP monkeys (Konitsiotis, 2000). Anti-parkinsonian actions of NMDA glutamate antagonists have also been reported in rodents and non-human primates (Steece-Collier et al., 2000). In a clinical study, an NMDA antagonist improved levodopa-induced dyskinesia (Verhagen Metman et al., 1998) and α2-adrenergic antagonists such as idazoxan and efaroxan improved symptoms of PD, particularly rigidity (Brefel-Courbon, 1998). Based on these study findings, we evaluated the effects of NBQX, MK-801 and idazoxan on the lateralization induced by unilateral lesion of the nigro-striatal dopaminergic system in rats. Much to our surprise, these compounds failed to improve imbalance of movement,
when they were administered alone. Although it is also important to test them in combination with levodopa, their use in monotherapy is unlikely to improve imbalance of motor function.

We have established a novel exploratory Y-maze test that easily detects lateralization in hemiparkinsonian rats. Our findings indicate that this method can detect anti-parkinsonian effects of nondopaminergic agents without the use of dopaminergic agents in combination. Furthermore, we can characterize the behavior using four indices. A key feature of the model is that we can distinguish lateralization (indicated as right%) from an increase of locomotion (detected as total counts in our system). Some medicines currently used for PD, e.g. levodopa and trihexyphenidyl, were found to improve lateralization in our system, while others were ineffective. The new pharmacological evaluation method that we have developed may therefore be useful in characterizing some aspects of the clinical efficacy of PD drugs. The method should contribute to the discovery of new anti-parkinsonian medicines and should be useful in studies of the mechanisms underlying the regulation of the dopaminergic system in the basal ganglia.
References


Footnote

Name and full address of person to receive reprint requests:

Makoto Nakagawa, Ph.D., Tsukuba Research Laboratories, Eisai Co., Ltd. 5-1-3, Tokodai, Tsukuba-shi, Ibaraki 300-2635, Japan
Legends for figures

Fig. 1. Schematic illustration of the exploratory Y-maze. A: Upper view of the Y-maze. The center of the maze is narrowed (8 cm width). Photo beams are indicated as broken lines. B: Side view of one arm of this maze. The ceiling of the center part is low (9.5 cm height).

Fig. 2. Behavioral analysis of 6-OHDA-lesioned rats in an exploratory Y-maze. Four weeks after the lesions, behavior was analyzed without administration of any drugs. The average of two behavior analyses is shown. The numbers of naive and lesioned rats were 15 and 71, respectively. *** < 0.001 compared to naive animals.

Fig. 3. Correlation between lateralization and dopamine content in the striatum (upper panel) and norepinephrine content in the frontal cortex (lower panel). The ordinate shows dopamine or norepinephrine level as a percentage of that in the intact side of the striatum or frontal cortex, respectively. Dopamine and norepinephrine contents in the intact side were 17,755 ± 281 and 1613 ± 405 ng/g of tissue, respectively. The abscissa shows right% measured in the exploratory Y-maze.

Fig. 4. Effects of levodopa, apomorphine and methamphetamine on behavior of 6-OHDA-lesioned rats. Levodopa and benserazide (4:1) were administered intraperitoneally 15 and 45 minutes before recording, respectively. Apomorphine was administered subcutaneously immediately before recording. Methamphetamine was
administered intraperitoneally 15 minutes before recording. The number of rats per group was 20 for the control and 8 for each group tested with levodopa, apomorphine or methamphetamine. *** < 0.001, ** < 0.01, * <0.05 compared to the control value.

Fig. 5. Effects of trihexyphenidyl and scopolamine on the behavior of 6-OHDA-lesioned rats. Trihexyphenidyl, scopolamine or N-methylscopolamine (NMS) was administered intraperitoneally 15 minutes before recording. The number of rats per group was 20 for the control and 12 for drug-treated animals. ** < 0.01, * <0.05 compared to the control value.

Fig. 6. Effects of NBQX, MK801 and idazoxane, on the behavior of 6-OHDA-lesioned rats. NBQX was administered immediately before recording. The other compounds were administrated intraperitoneally 15 minutes before recording. The numbers of rats per group were 6 in the idazoxane study and 8 in the MK801 and NBQX studies. * <0.05 compared to control value.
Figure 1
The diagram shows two sections labeled A and B with various dimensions:

- **Section A**:
  - Beam sensor connected to 18 cm length.
  - Vertical line 11 cm.
  - 30 cm length.

- **Section B**:
  - Beam sensor connected to 12 cm length.
  - Vertical line 4 cm.
  - 9.5 cm length.
Figure 2
Figure 3
Figure 6