ENHANCEMENT OF APOMORPHINE-INDUCED ROTATIONAL BEHAVIOUR IN RATS FOLLOWING THE COMBINATION OF 6-HYDROXYDOPAMINE AND ELECTROLYTIC LESIONS IN THE SUBSTANTIA NIGRA

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Accepted August 7, 1978

Abstract—Electrolytic lesion in combination with 6-hydroxydopamine (6-OHDA) microinjection was produced in rat substantia nigra (SN) and the animals were observed for drug-induced rotational behaviour. Apomorphine produced rotation toward the left (contralateral) while methamphetamine produced rotation toward the right (ipsilateral) in rats with 6-OHDA lesion of the right SN. Both apomorphine and methamphetamine produced rotations ipsilateral to the side of the lesion in rats with unilateral electrolytic lesion of the SN. When the electrolytic lesion was placed in the right SN in an animal that had been treated with 6-OHDA (group 3), apomorphine-induced rotation toward the left was markedly suppressed. Methamphetamine-induced rotation was not affected by this treatment. When the electrolytic lesion was placed in the left SN of rats with 6-OHDA lesion of the right SN (group 4), apomorphine-induced rotation toward the left was significantly enhanced. Methamphetamine-induced rotation obviously decreased. The results in group 3 indicate that electrolytic lesion may induce a dysfunction of postsynaptic factors (i.e. efferent pathways and dopamine receptors) in addition to the degeneration of the nigrostriatal dopaminergic pathway, which may indicate a difference in the direction of apomorphine-induced rotation in groups 1 and 2. The enhancement of rotation produced by apomorphine in group 4 appears to be the result of a dysfunction of the postsynaptic factors in the left SN in combination with the denervation supersensitivity to apomorphine in the right striatum.

The injection of 6-hydroxydopamine (6-OHDA) into the unilateral substantia nigra (SN) of the rat has been reported to induce a degeneration of the nigrostriatal dopaminergic neurons, which results in a decrease in dopamine (DA) content in the ipsilateral striatum (1, 2). When apomorphine, a dopaminergic receptor stimulating agent, was given a few days after 6-OHDA injection, the animal rotated toward the unoperated side. The rotational behaviour was shown to be produced by an imbalance of the stimulation of DA receptor in the bilateral striatum (2, 3). The contralateral rotation induced by apomorphine was considered to be due to the dominant stimulation on the receptor with denervation supersensitivity in the lesioned side of the striatum (2). Amphetamine, which released DA from the nerve endings of dopaminergic neurons on the normal side of the striatum, produced ipsilateral rotation (4, 5).

On the other hand, both apomorphine and amphetamine induced rotation toward the operated side in the rat with an electrolytic lesion in the unilateral SN. The ipsilateral rotation produced by apomorphine was suggested to be due to the dominant effect on the
receptor in the normal striatum, since the denervation supersensitivity might not develop in the striatum of the operated side following electrocoagulation (6, 7). However, it has not been unequivocally demonstrated that the direction of the apomorphine-induced rotation in the rat with the unilateral electrolytic lesion of the SN is the reverse of that in the animal with 6-OHDA lesion.

The present experiment was designed to investigate the effect of electrolytic lesion on drug-induced rotational behaviour in rats with unilateral 6-OHDA lesion of the SN. We found disappearance of the sensitivity to apomorphine when the electrolytic lesion of the SN was placed ipsilateral to, and enhancement when it was placed opposite to, the side of 6-OHDA lesion, respectively.

MATERIALS AND METHODS

Wistar and Donryu rats weighing between 150 and 180 g at the time of the stereotaxic operations were housed under conditions of uniform humidity, temperature and lighting (on 0700, off 1900).

Injection of 6-OHDA into the unilateral SN

Under pentobarbital anesthesia the head of the rat was positioned on the stereotaxic apparatus and injection of 6-OHDA was performed through a stainless steel pipe 0.4 mm in outer diameter connected to a Gilmont micrometer syringe according to the method of Ungerstedt (2). 6-OHDA 8 μg dissolved in sterile saline containing ascorbic acid 0.5 mg/ml was injected into the SN in a volume of 4 μl at the rate of 1 μl/min after which the syringe was left in place for an additional 1 min. The stereotaxic coordinates of the injection site were A: 2.4, L: 1.8, H: -2.5 according to the rat brain atlas (8).

Electrolytic lesion of the SN

Unilateral electrolytic lesion of the SN (A: 2.0, L: 1.8, H: -2.5) was produced in the animal anesthetized with pentobarbital and positioned in the stereotaxic instrument. A lesion producing device (Stoelting Co., Chicago) was used to deliver anodal direct current (2 mA for 10 sec) through the epoxy-insulated stainless steel electrode (0.5 mm in the outer diameter), bared 0.3 mm at the tip, with the stereotaxic frame serving as the inert electrode.

Measurement of the drug-induced rotational behaviour

A rat was placed in a plastic cage with dimensions of 30 × 35 × 17 cm³ and left undisturbed for adaptation to the cage for 10 min. Rotational behaviour was directly observed for 1 to 2 hr; a 360° turn was considered as one rotational count. Apomorphine HCl (Merck) and methamphetamine HCl (Dainippon Seiyaku) were dissolved in saline and administered subcutaneously. The dose of the drug was expressed as a salt. Rats were given apomorphine 1.25 mg/kg at 10-14 days after the operation and the animals that showed the rotational behaviour were used in the present experiment. Apomorphine 0.16 mg/kg produced stable rotational behaviour which lasted for nearly 60 min in the animals of group 1, 3-6 weeks after 6-OHDA lesion, while a small number of rotations resulted within 30 min in group 2. Therefore, the effect of apomorphine at 0.16 mg/kg was estimated in groups
The animals in groups 3 and 4 were given apomorphine and methamphetamine at 21-24 days and an electrolytic lesion was placed on each side of the SN at 25 days after 6-OHDA injection. The drug-induced rotation was estimated again 7-10 days after the electrolytic lesion.

**Estimation of monoamine content and histochemistry**

Forty-eight hours after observation of rotational behaviour the animals were decapitated. The caudate-putamen, 64±1.9 mg wet weight (n=20), and the neocortex, 226±5.5 mg/kg wet weight (n=20), were dissected out for estimation of monoamine content, and the brainstem was prepared for histochemical analysis. In some instances the brain was separated into the forebrain and brainstem which were prepared for fluorescence histochemistry. Catecholamines were extracted with acidified n-butanol and measured fluorometrically according to a modification of Hogan's method (quoted in refs. 9, 10, 11). Serotonin was assayed according to the method of Maickel et al. (12). For the histochemistry the brain was frozen in isopentane cooled in liquid nitrogen and freeze-dried for 3 days. The specimens were then exposed to formaldehyde gas at 70°C for 2 hr, embedded in paraffin, sectioned at 10 μ and mounted in Entellan-xylene mixture (10:1) on microscope slides (13). The catecholamine fluorescence was observed through an Olympus fluorescence microscope with a high pressure mercury lamp. The light was filtered through a BV excitation filter and Y-515 filter. A fluorescence micrograph was made with Kodak Tri-X film, at 3 to 5 min exposure and the results were drawn following the atlas of König and Klippel (8) in the light of the results of Jacobowitz and Palkovitz (14).

**RESULTS**

The various groups of animals with 6-OHDA and/or electrolytic lesions in the SN and the direction of the rotational behaviour induced by apomorphine and methamphetamine are shown in Table 1. To examine effects of electrolytic lesion on drug-induced rotational behaviour in rats with 6-OHDA lesion in the right SN, the electrolytic lesion was placed in the right SN in group 3 and in the left SN in group 4, respectively. 6-OHDA or electrolytic lesion was made in the unilateral SN as in groups 1 and 2, in order to compare with groups 3 and 4.

| Group | Injection or Lesion | The Lesioned Side | The Direction of the Rotation induced by |
|-------|---------------------|------------------|----------------------------------------|
|       |                     |                  | Apomorphine | Methamphetamine |
| 1     | 6-OHDA              | right            | left        | right           |
| 2     | Electrolytic        | right            | right       | right           |
| 3     | 6-OHDA + Electrolytic | right   | right       | right           |
| 4     | 6-OHDA + Electrolytic | left    | left        | right or left   |

| Table 1. Lesioned side and direction of rotational behaviour induced by apomorphine and methamphetamine |
Drug-induced rotational behaviour was estimated at 21–24 days after 6-OHDA lesion. Apomorphine at the dose of 0.16 mg/kg produced a rotation toward the left 3 to 4 min after the injection, and the rotational behaviour lasted for nearly 60 min as shown in Fig. 1. At the dose of 0.32 and 0.64 mg/kg, apomorphine produced long-lasting rotation. The mean of the total turns for 1 hr following apomorphine 0.16–0.64 mg/kg was 200 to 300. Some of the animals showed behaviour such as biting and pulling the hair of their backs or left hind legs, during the rotation. Methamphetamine at the doses of 1.25 and 2.5 mg/kg produced a marked rotation toward the right. The rotational behaviour appeared 10 min after the injection and lasted over 2 hr. Methamphetamine 0.63 mg/kg produced locomotor activation as well as the rotation during 2 hr of observation. The total turns for 2 hr at the doses of 0.63, 1.25 and 2.5 mg/kg increased in a dose-dependent manner. Locomotor activation was observed only for the initial 30 min at the dose of 2.5 mg/kg, while such was intermittently observed during 2 hr at the doses of 0.63 and 1.25 mg/kg. Piloerection was quite evident for 2 hr after methamphetamine. No rotation occurred with the administration of saline during the 2 hr observation period.

Group 2

The animals were given drugs 14 days after the lesioning. Apomorphine at the doses of 0.16 to 1.25 mg/kg produced rotation toward the right 4–5 min after the injection. As shown in Fig. 2, the rotational behaviour lasted over 60 min after the administration of a high dose (1.25 mg/kg), while after a low dose (0.16 mg/kg) such disappeared within 30 min. The total turns for 1 hr increased in a dose-dependent manner. Methamphetamine at the doses of 2.5 and 5 mg/kg produced a marked rotation toward the right. The rotation appeared 15 min after the injection and lasted over 2 hr. Methamphetamine 1.25 mg/kg
FIG. 2. Rotational behaviour induced by apomorphine and methamphetamine in group 2. Both apomorphine 0.16 mg/kg (---○---) and 1.25 mg/kg (---○---) (upper left) and methamphetamine 2.5 mg/kg (---○---) and 5 mg/kg (---○---) (lower left) produced the ipsilateral turning. Total turns counted for 1 hr after apomorphine (upper right) and for 2 hr after methamphetamine (lower right). Other expressions are the same as those in Fig. 1.

produced the rotation toward the right and left in one animal, although the total turns of each direction were less than 50. Methamphetamine induced marked locomotor activation at the doses of 1.25 and 2.5 mg/kg and piloerection was evident during the observation period. There was no rotation after the administration of saline during the 2 hr observation period.

*Group 3*

Apolomorphine 0.16 mg/kg produced a rotation toward the left before the addition of the electrolytic lesion in animals with unilateral 6-OHDA lesion. After the electrolytic lesion had been placed in the right SN with 6-OHDA lesion, the rate of turns was obviously suppressed as shown in Fig. 3. The total turns for 1 hr decreased markedly as compared with those before the addition of the electrolytic lesion (Table 2). The direction of the rotation induced by apomorphine reversed in three out of six animals. Methamphetamine was administered at the dose of 2.5 mg/kg to groups 3 and 4. Methamphetamine produced marked rotation toward the right in animals with unilateral 6-OHDA lesion. After the electrolytic lesion had been placed in the right SN, methamphetamine induced rotation toward the right. There were no significant differences in the rate of turns and total turns before and after the addition of the electrolytic lesion (Fig. 3 and Table 2). When the electrolytic lesion was placed in a more medial region than the SN at the coordinates, A: 2.0, L: 0.8, H: -2.5, the rotational behaviour induced by apomorphine and methamphetamine was not affected. No rotation was produced by the administration of saline for 2 hr in this group.

*Group 4*

Since the animals do not eat or drink spontaneously after bilateral lesions of the SN with electrolytic and 6-OHDA lesions, the animals of all groups shown in Table 2 were fed a liquid diet through an intragastric tube twice a day after the electrolytic lesioning.
the electrolytic lesion had been placed in the SN opposite the 6-OHDA lesion, the animals rotated toward the side of the electrolytic lesion following the administration of apomorphine. For 1 hr, the rate of turns and the total turns induced by apomorphine were enhanced after electrolytic lesion as compared with those obtained in the animals before electrolytic lesion (Fig. 4 and Table 2). The animals in group 1 which had been fed a liquid diet, as a control, showed an increase in apomorphine response in the range of 0-25%. When the animals

### Table 2. Total turns induced by apomorphine and methamphetamine before and after electrolytic lesioning in animals with unilateral 6-OHDA injections of the SN.

| Group | No. of rats | Total Turns Before Electrolytic Lesion | Total Turns After Electrolytic Lesion |
|-------|-------------|----------------------------------------|---------------------------------------|
|       |             | Apomorphine HCl 0.16 mg/kg, s.c.       |                                       |
| 3     | 6           | 191 ± 48                               | 20 ± 42**                             |
| 4     | 7           | 186 ± 33                               | 365 ± 24**                            |
|       |             | Methamphetamine HCl 2.5 mg/kg, s.c.    |                                       |
| 3     | 6           | 816 ± 114                              | 600 ± 153                             |
| 4     | 6           | 765 ± 152                              | 166 ± 100**                           |

Total turns counted for 1 hr after apomorphine and for 2 hr after methamphetamine. **P<0.01.
in group 4 were given methamphetamine, the direction of the rotation was not constant. The rate of turns and the total turns for 2 hr significantly decreased as compared with the control. Some of the animals in group 4 showed a spontaneous rotation toward the left for 2-3 min when they were placed in a new environment. When electrolytic lesion was applied to a more medial region than the SN at the coordinates, A: 2.0, L: 0.8, H: -2.5, apomorphine-induced rotation was not affected. The total turns for 2 hr following the administration of saline were less than 20 in the animals of group 4.

**Tissue monoamine content and histochemistry**

As shown in Table 3, DA was not detected in the ipsilateral caudate-putamen of the rats that had been given 6-OHDA into the unilateral SN. After electrolytic lesioning, DA content in the lesioned side of the caudate-putamen was about 10-20% of that in the control side. DA content in the cerebral cortex was 10-25% of the control after 6-OHDA lesion and it was 40-50% of the control after electrolytic lesion. Noradrenaline (NA) content in the caudate-putamen and the cerebral cortex markedly decreased after 6-OHDA lesion. NA in the caudate-putamen was 40-65% after electrolytic lesion, while it was little affected in the cerebral cortex following electrolytic lesion. There was no change in the serotonin content of the caudate-putamen and the cerebral cortex after 6-OHDA and electrolytic lesions.

Fluorescence histochemical examination showed a total loss of striatal and nigral fluorescence of the side of the 6-OHDA lesion. A section from the animals in group 4 is shown in Fig. 5. Some of the fluorescent cells remained in the ventromedial part of the SN after electrolytic lesioning. The site of lesioning in the SN was centered in the ventromedial area of the zona compacta. Lemniscus medialis, fasciculus retroflexus and pedunculus corporis mamilaris were partly damaged. The lesion extended anteriorly to the level of the Nucl. mamillaris medialis, pars medialis and posteriorly to the anterior border of the Nucl. pontis.

**Table 3. Contents of catecholamines in the caudate-putamen and cerebral cortex of the rat with 6-OHDA and electrolytic lesions**

| Group          | No. of rats | Dopamine^a |   | Noradrenaline^a |   |
|---------------|-------------|------------|---|-----------------|---|
| Caudate-Putamen | 1           | 8          | 10.38±0.60 | 0^b | 0.34±0.03 | 0.06±0.02^e |
|               | 2           | 6          | 9.24±0.105 | 1.08±0.32^c | 0.32±0.03 | 0.14±0.02^e |
|               | 3           | 5          | 10.50±0.30 | 0^b | 0.34±0.03 | 0.04±0.02^e |
|               | 4           | 5          | 2.29±0.22  | 0^b | 0.22±0.02 | 0.06±0.02^e |
| Cerebral Cortex | 1           | 8          | 1.21±0.16  | 0.14±0.04^c | 0.36±0.01 | 0.05±0.01^e |
|               | 2           | 6          | 0.96±0.19  | 0.43±0.05^d | 0.35±0.03 | 0.30±0.02 |
|               | 3           | 5          | 0.94±0.07  | 0.23±0.03^c | 0.38±0.03 | 0.10±0.03^e |
|               | 4           | 5          | 0.49±0.05  | 0.12±0.05^e | 0.41±0.02 | 0.09±0.03^e |

^a: pg/g wet tissue. ^b: DA was not detectable in the tissue. ^c: P<0.01. ^d: P<0.05
Ungerstedt and Arbuthnott (15) recorded the rotation with the rotometer in the hemispherical perspex bowl. Some of workers observed rotational behaviour in the caged animals and estimated the intensity of the rotation with the rank-scoring method as described by Naylor and Olley (16). In our preliminary work, we found that the rotational behaviour induced by apomorphine could be measured similarly by either method, but following the administration of methamphetamine a considerably greater number of rotations occurred using the hemispherical bowl method. When methamphetamine was given to an animal in the cage, a low dose (0.625 and 1.25 mg/kg) produced locomotor activation as well as rotation while a high dose (2.5 mg/kg) usually resulted in rotational behaviour. A locomotor activation induced by a low dose of methamphetamine in the cage was observed as a rotation in the bowl. Therefore, in the present experiment, rotational behaviour was directly observed in the rectangular cage. In the present study, apomorphine produced a rotation contralateral to the side of the 6-OHDA lesion, while methamphetamine induced a ipsilateral rotation in group 1. Both apomorphine and methamphetamine induced rotation ipsilateral to the side of the electrolytic lesion in group 2. These results corresponded to those of other workers (2, 4–6, 17). The direction of the rotation induced by apomorphine was exactly opposite in groups 1 and 2.

To investigate the mechanism by which apomorphine induces ipsilateral rotation in group 2, the electrolytic lesion was placed in the right SN in animals that had been given
6-OHDA. In the animals in which the contralateral rotation was produced by apomorphine after 6-OHDA lesion of the right nigrostriatal dopaminergic pathway, placement of the electrolytic lesion on the same side of the SN markedly suppressed the apomorphine-induced rotation or reversed the direction of the rotation. Methamphetamine-induced response was not affected even in cases of electrolytic lesioning. When the electrolytic lesion was placed in a more medial region than the SN at the coordinate (L=0.8), the rotational behaviour induced by apomorphine or methamphetamine was not affected. The result indicates that decrease of the apomorphine-induced rotation in group 3 is not due to the non-specific brain lesion. Moreover, the results suggest the possibility that electrolytic lesioning affects the following factors in addition to the degeneration of the nigrostriatal dopaminergic neurons; (I) lesion of an efferent pathway that is required for the contralateral rotation and (II) an impairment of DA receptor on the postsynaptic site of the nigrostriatal dopaminergic neuron in the right striatum. Such destruction induced by electrolytic lesioning may lead to rotation toward the right due to the dominant effect of apomorphine in the left striatum of the animal in group 2. Ungerstedt and Marshall (18) found that administration of apomorphine resulted in a resumption of drinking in animals with an adipsia after lesions had been induced by 6-OHDA of bilateral ascending dopaminergic neurons, while classical lateral hypothalamic syndromes induced by electrocoagulation were not affected by apomorphine. From these results, they suggested that the adipsia produced by 6-OHDA lesioning and electrocoagulation was due to lesions in the afferent and efferent pathways, respectively. In the animal with a denervation supersensitivity following an unilateral 6-OHDA lesioning of the ascending dopaminergic neurons, a low dose of apomorphine preferentially stimulated the DA receptor and induced a pronounced rotational behaviour in the direction contralateral to the lesion. Lateral hypothalamic electrocoagulation and 6-OHDA injection resulted in 80% inhibition of the rotation. Ungerstedt and Marshall proposed that the lesion of the hypothetical strio-pallidal efferent fiber which is localized in the region of lateral hypothalamus concealed the effect of apomorphine on the denervated DA receptors (18).

The electrolytic lesion placed in the SN in the present study did not affect the lateral hypothalamus. It has been reported that input from a higher center into the SN includes corticonigral fiber (19) and strionigral fiber (20-22). The function of the strionigral fiber was inhibitory (23), and the transmitter was suggested to be GABA (24). The efferent pathways from the SN were found to be nigrostriatal fiber which contained DA (25-27), nigropallidal fiber (28) and nigroreticulocerebellar fiber (29) and the latter was mainly transmitted at the midbrain reticular formation and descended to the motor neuron in the anterior horn of the spinal cord. The injection of 6-OHDA into the area of the SN relatively selectively degenerated the nigrostriatal dopaminergic neurons, while the electrolytic lesion impaired not only the nigrostriatal dopaminergic pathway but also afferent and efferent pathways as described above in the SN region. However, from the present study it is not clear which pathway significantly affected the rotational behaviour.

The factor (II) may be supported by the following reports. Spehlmann (30) showed
that inhibitory effects of DA following the microiontophoretic application in the striatum were mitigated by lesions in the ventromedial tegmentum which resulted in the reduction of DA content in that nucleus. Since contralateral asymmetric behaviour produced by unilateral intrastral injection of DA was abolished by chronic electrolytic lesion of the SN on the same side as the injection, Costall et al. (6) explained as due to hyposensitivity of striatal DA receptors their results that prior electrolytic lesion of the SN abolished contralateral circling behaviour induced by apomorphine in rats with 6-OHDA lateral hypothalamic lesions. The present result obtained in group 3, as well as the results reported by Ungerstedt and Marshall (18), may be interpreted by the factor (II). The results from group 3 provide an explanation for the difference of the direction of the apomorphine-induced rotation in groups 1 and 2. Rotation towards the right following the administration of apomorphine in group 2 appears to be due to the factors mentioned above.

When the electrolytic lesion was produced in the left SN of rats with 6-OHDA lesion in the right nigrostriatal dopaminergic system (group 4), methamphetamine-induced rotation was suppressed markedly. This result may be due to decrease of DA from the nerve endings on each side of the striatum. We found the enhancement of the apomorphine-induced rotational behaviour in the animals of group 4. In addition to the denervation supersensitivity of DA receptors in the right striatum, the dysfunction of the left efferent pathways and of DA receptors should result in an enhancement of the rotation induced by apomorphine. There is a report suggesting that the left and right nigrostriatal dopaminergic pathways do not function independently but are closely related to each other (31). The fact that the duration of spontaneous rotation induced by the transfer of an animal into the new environment was longer in group 4 than in group 1 indicates that the interaction of both pathways was removed by the placement of the electrolytic lesion in the SN of the side contralateral to the 6-OHDA lesion. It was reported that apomorphine-induced rotation in rats with unilateral striatal lesions was enhanced by bilateral or unilateral lesions of dopaminergic nerve terminals in the Nucl. accumbens following the microinjection of 6-OHDA (32, 33). Although the results are quite similar to the response in group 4, the sensitivity to apomorphine is different in those animals. Marshall and Ungerstedt (34) applied electrocoagulation in the right internal capsule at the level of the hypothalamus in the animals with 6-OHDA lesion of the left SN. The intensity of the rotation induced by apomorphine was not affected by such coagulation which in itself induces a lesion on both afferent and efferent pathways in the right strionigral complex. The difference between the present study and their results is not clear. Since the animals with bilateral lesions in the SN showed the adipsia, the animals of groups 3, 4 and the control group were fed a liquid diet. Thus the enhancement of the apomorphine-induced response would appear to be derived from the inhibition of apomorphine metabolism in group 4. However, this possibility can be excluded from the fact that the electrolytic lesion enhanced the rate of rotation but not the duration of the response. Biochemical data in the present experiment indicate that the noradrenergic mechanism may play a role partly in drug-induced rotational behaviour in groups 1 and 2 but may not be related to the disappearance and the enhancement of apomorphine-induced
rotation in groups 3 and 4, respectively.

Acknowledgements: This work was supported by grant No. 144074 from the Ministry of Education, Science and Culture, Japan. Thanks are due to Miss M. Ikeda for excellent technical assistance and to Ms. C. Utech for assistance with the manuscript.

REFERENCES

1) UNGERSTEDT, U.: 6-Hydroxydopamine-induced degeneration of central monoamine neurons. Europ. J. Pharmacol. 5, 107-110 (1968)

2) UNGERSTEDT, U.: Postsynaptic supersensitivity after 6-hydroxydopamine-induced degeneration of the nigrostriatal dopamine system. Acta physiol. scand. Suppl. 367, 69-93 (1971)

3) UNGERSTEDT, U., BUTCHER, L.L., BUTCHER, S.G., ANDEN, N.-E. AND FUXE, K.: Direct chemical stimulation of dopaminergic mechanisms in the neostriatum of the rat. Brain Res. 14, 461-471 (1969)

4) UNGERSTEDT, U.: Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behaviour. Acta physiol. scand. Suppl. 367, 49-68 (1971)

5) MARSDEN, C.A. AND GULDENBERG, H.C.: The role of monoamines in rotation induced or potentiated by amphetamine after nigral, raphe and mesencephalic reticular lesions in the rat brain. Neuropharmacol. 12, 195-211 (1973)

6) COSTALL, B., MARSDEN, C.D., NAYLOR, R.J. AND PYCOCK, C.I.: The relationship between striatal and mesolimbic DA dysfunction and the nature of circling responses following 6-OHDA and electrolytic lesions of the ascending DA systems of rat brain. Brain Res. 118, 87-113 (1976)

7) IWAMOTO, E.T., LOH, H.H. AND WAY, E.L.: Circling behaviour in rats with 6-OHDA or electrolytic nigral lesion. Europ. J. Pharmacol. 37, 339-356 (1976)

8) KÖNIG, J.F.R. AND KLIPPPEL, R.A.: The rat brain. A stereotaxic Atlas of the Forebrain and lower Parts of the Brain Stem. Williams and Wilkins, Baltimore (1963)

9) JACOBOWITZ, D., COOPER, T. AND BARNER, N.B.: Histochemical and chemical studies of the localization of adrenergic and cholinergic nerves in normal and denervated cat hearts. Circulation Res. 20, 289-298 (1967)

10) RICHARDSON, J.S. AND JACOBOWITZ, D.M.: Depletion of brain noradrenaline by intraventricular injection of 6-hydroxynorepinephrine: A biochemical, histochemical and behavioural study in rats. Brain Res. 58, 117-133 (1973)

11) WATANABE, H.Y. AND WATANABE, K.: The effect of lowering the serotonin content of the rat brain on spontaneous locomotor activity. Chem. Pharm. Bull., Tokyo 23, 1192-1196 (1975)

12) MAICKEL, R.P., COX, JR., R.H., SAILENT, J. AND MILLER, F.P.: A method for the determination of serotonin and norepinephrine in discrete areas of rat brain. Int. J. Neuropharmacol. 7, 275-281 (1968)

13) FALCK, B. AND OWMAN, C.: A detailed methodological description of the fluorescence method for the cellular demonstration of biogenic monoamines. Acta Univ. Lund. sect II, No. 7, p.1-23 (1965)

14) JACOBOWITZ, D.M. AND PALKOVITZ, M.: Topographic atlas of catecholamine and acetylcholinesterase-containing neurons in the rat brain. J. comp. Neurol. 157, 13-28 (1974)

15) UNGERSTEDT, U. AND ARBUTHNOTT, G.W.: Quantitative recording of rotational behaviour in rats after 6-hydroxydopamine lesions of the nigrostriatal dopamine system. Brain Res. 24, 485-493 (1970)

16) NAYLOR, R.J. AND OLLEY, J.E.: Modification of the behavioural changes induced by amphetamine in the rat by lesions in the caudate nucleus, caudate-putamen and globus pallidus. Neuropharmacol. 11, 91-99 (1972)

17) CHRISTIE, J.E. AND CHOW, T.I.: Turning behaviour as an index of the action of amphetamines and ephedrines on central dopamine-containing neurons. Brit. J. Pharmacol. 43, 658-667 (1971)
18) UNGERSTEDT, U. AND MARSHALL, J.: Nerve degeneration in functional studies: Experiments illustrating the problem of lesion specificity and compensatory supersensitivity. Chemical Tools in Catecholamine Research, Edited by JONSSON, G., MALMFORS, T. AND SACHS, Ch., Vol. I, p.311–318, North-Holland Pub. Co., Netherlands (1975)

19) RINVIK, E.: The cortico-nigral projection in the cat. An experimental study with silver impregnation methods. J. comp. Neurol. 126, 241–254 (1966)

20) SZABÓ, J.: Projections from the body of the caudate nucleus in the rhesus monkey. Exp. Neurol. 27, 1–15 (1970)

21) GROFOVA, I. AND RINVIK, E.: An experimental electron microscopic study on the strionigral projection in the cat. Exp. Brain Res. 11, 249–262 (1970)

22) NIIMI, K., IKEDA, T., KAWAMURA, S. AND INOSHITA, H.: Diferent projections of the head of caudate in the cat. Brain Res. 21, 327–343 (1970)

23) YOSHIDA, M. AND PRECHT, W.: Monosynaptic inhibition of neurons of the SN by caudate-nigral fibers. Brain Res. 32, 225–228 (1971)

24) OBATA, K. AND YOSHIDA, M.: Caudate-evoked inhibition and action of GABA and other substances on cat pallidal neurons. Brain Res. 64, 455–459 (1973)

25) CARPENTER, M.B. AND MCMASTER, R.E.: Lesions of the SN in the rhesus monkey. Efferent fiber degeneration and behavioral observations. Am. J. Anat. 114, 293–320 (1964)

26) IBATA, Y., NOJO, Y., MAISUERA, T. AND SANO, Y.: Nigro-neostriatal projection. A correlative study with Fink-Heimer impregnation, fluorescence histochemistry and electron microscopy. Z. Zellforsch. 138, 333–344 (1973)

27) ANDEN, N.-E., CARLSSON, A., DAHLSTRÖM, A., FUXE, K., HILLARP, N.A. AND LARSSON, K.: Demonstration and mapping out of nigro-neostriatal dopamine neurons. Life Sci. 3, 522–530 (1964)

28) CARPENTER, M.B. AND STROMINGER, N.L.: Efferent fibers of the subthalamic nucleus in the monkey. A comparison of the efferent projections of the subthalamic nucleus, SN and globus pallidus. Am. J. Anat. 121, 41–72 (1967)

29) WOODBURN, R.T., CROSBY, E.C. AND MCCOTTER, R.E.: The mammalian midbrain isthmus regions. Part II. The fiber connection. A. The relations of the tegmentum of the midbrain with the basal ganglia in the macaca mulatta. J. comp. Neurol. 85, 67–92 (1946)

30) SPEHLMANN, R.: The effects of acetylcholine and dopamine on the caudate nucleus depleted of biogenic amines. Brain 98, 219–230 (1975)

31) NIEUOLLON, A., CHÉRAMY, A. AND GLOWINSKI, J.: Interdependence of the nigrostriatal dopaminergic systems on the two sides of the brain in the cat. Science 198, 416–418 (1977)

32) KELLY, P.H. AND MOORE, K.E.: Mesolimbic dopaminergic neurons in the rotational model of nigrostriatal function. Nature 263, 695–696 (1976)

33) PYCOCK, C.J. AND MARSDEN, C.D.: The rotating rodent: A two component system? Europ. J. Pharmacol. 47, 167–175 (1978)

34) MARSHALL, J.F. AND UNGERSTEDT, U.: Supersensitivity to apomorphine following destruction of the ascending dopamine neurons: Quantification using the rotational model. Europ. J. Pharmacol. 41, 361–367 (1977)