# BEHAVIOURAL–ANATOMICAL CORRELATES OF CENTRAL CATECHOLAMINE NEURONS

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THE ASCENDING catecholamine (CA) pathways may be subdivided into a few major neuron systems (FUXE, 1965; UNGERSTEDT, 1971a; MAEDA and SHIMIZU 1972). The ventral noradrenaline (NA) bundle (including the intermediate bundle) arising from cell groups in the medulla and pons and terminating in the mesencephalon, the hypothalamus and the preoptic area. The dorsal NA bundle arising from the locus coeruleus proper and terminating in the cerebellar and cerebral cortices, the hippocampus and probably also in several subcortical areas, e.g. the reticular formation, the thalamus and the hypothalamus. The nigro-striatal dopamine (DA) system originating in the zona compacta of the substantia nigra and terminating in the striatum (nucl. caudatus and putamen) and the meso-limbic DA system arising from cell bodies dorsal and lateral to the interpeduncular nucleus and terminating in the nucleus accumbens and the olfactory tubercle.

The anatomy of the CA cell groups and axon bundles permits the localisation of lesions interrupting certain pathways while leaving others intact. The ventral and dorsal NA bundles may be lesioned separate from each others and caudal to the DA cell groups. The striatal and the limbic DA systems may also be separated by lesions but the lesions will always cause some damage to the ascending NA axons. However, the extent of the DA lesion may be kept constant by positioning lesions along the DA pathway, while the involvement of the NA lesion is varied in this way.

The specificity of the lesion technique may be considerably increased by the use of intracerebral, stereotaxic injections of 6-hydroxydopamine (6-OH-DA) (UNGERSTEDT, 1968; 1971a, 1973). The NA and DA neurons are lesioned with great selectivity while the unspecific lesion is limited to a narrow zone around the tip of the cannula (UNGERSTEDT, 1971b; HÖKFELT and UNGERSTEDT, 1973). We have used stereotaxic injections of 6-OH-DA into the rat brain with drugs affecting CA transmission and quantitative analysis of behaviour in order to gain an understanding for the involvement of CA neurons in the control of behaviour. The combination of drugs and lesions has permitted us to study the effects of hyper- as well as hypofunction in a certain CA neuron system.

## DOPAMINE NEURONS

A unilateral 6-OH-DA induced lesion of the nigro-striatal DA pathway induces profound changes in movements and posture (UNGERSTEDT, 1968). The rat deviates towards the side of the lesion and amphetamine induced release of DA from the non-lesioned DA system changes the deviation into continuous circling movements toward the lesioned side. We have constructed a "rotometer" consisting of a bowl, shaped as a hemisphere, where the animal moves connected by a thin wire to the recording device (UNGERSTEDT and ARBUTHNOTT, 1970). Pharmacologically

induced DA release induces a dose dependent rotational behaviour toward the lesioned side (UNGERSTEDT, 1971c) while DA receptor stimulating drugs, like apomorphine, (ERNST, 1967, ANDÉN *et al.*, 1967) induce a rotation in the opposite direction (UNGERSTEDT, 1971d). The direction of the rotational behaviour seem to reveal on which side the DA receptors are most activated. DA releasing drugs as well as DA receptor stimulating drugs cause rotation towards the lesion after unilateral damage of the striatum (ANDÉN *et al.*, 1965) and unilateral injection of DA into the striatum induces rotation towards the side opposite the injection, i.e. away from the most activated side (UNGERSTEDT *et al.*, 1969). In the unilaterally 6-OH-DA denervated animal apomorphine induces rotation towards the intact side indicating that the denervated side is "supersensitive" to apomorphine. In fact, iontophoretic application of apomorphine (HOFFER *et al.*, 1973) or DA (FELTZ and CHAMPLAIN, 1973) shows that the denervated striatal cells are more sensitive to apomorphine and DA than the innervated.

Bilateral 6-OH-DA induced degeneration of the nigro-striatal DA system induces a state of akinesia, catalepsia, adipsia and aphagia. The animals die if not supported by tube feeding. The syndrome is closely similar to the "lateral hypothalamus lesion" syndrome which has been attributed to the degeneration of an eating and drinking centre in the lateral hypothalamus (ANAND and BROBECK, 1951). However, recent studies with histochemical technique show that lateral hypothalamic lesions interrupt the nigro-striatal DA system and thus denervates the striatum (UNGERSTEDT, 1970, 1971e). It seems highly probable that the lateral hypothalamic adipsia and aphagia is due to interference with striatal rather than hypothalamic function. The severity of the syndrome seems related to the completeness of the DA denervation. The less DA that remains in the striatum the less likely is the animal to resume eating and drinking. Animals with no DA nerve terminals detectable in the striatum and no DA cell bodies in the substantia nigra show no sign of recovery even after 6 months of tube feeding (AVEMO *et al.*, 1973). Such animals show no response to amphetamine (2 mg/kg) but a supersensitive response to apomorphine which is in accordance with the findings in the unilaterally denervated animal.

In order to further link the syndrome of akinesia, adipsia and aphagia to the degeneration of DA neurons, we have substituted the lost DA with a low dose of apomorphine: normal animals were trained to run a maze for water reward. When fully trained the DA neurons were bilaterally degenerated with 6-OH-DA. The lesion completely abolished all responses in the maze. However, after a low dose of apomorphine (0·1 mg/kg) the animals were able to run the maze and consume the water (LJUNGBERG and UNGERSTEDT 1973). Too high a dose of apomorphine introduced stereotyped behaviour and decreased or abolished the maze performance. The fact that bilateral removal of the DA system abolished a previously learned response may in this case be related to the akinesia and not to any interference with learning processes. To test this, we developed an under-water Y-maze (RANJE and UNGERSTEDT, 1973). Rats were forced under the water surface in the start box, swam to the choice point and had to select the lit up arm in order to reach the surface. The position of the arm was altered. Fully trained animals were bilaterally DA denervated. They still performed in the maze being slightly slower than controls but not significantly different as regards errors. It is interesting that the animals were, in fact, able to overcome their akinesia in this situation of "high motivation".

There is an obvious parallel in the "paradoxical kinesia" observed in similar situations in Parkinson degeneration of DA neurons.

In search for the functional deficit common to the rotating, unilaterally denervated animal, as well as the bilaterally denervated akinetic, adipsic and aphagic animals, we have examined their ability to react, i.e. orient towards sensory stimuli. A unilaterally DA denervated animal does not orient towards any visual, olfactory, auditory or tactile stimuli applied to the side of the body contralateral to the degeneration of the DA neurons (LJUNGBERG and UNGERSTEDT, 1973). He gradually recovers his ability to orient towards stimuli, however, the inability to orient towards tactile stimuli seems permanent. The fact that the animals are able to orient towards certain sensory stimuli but not towards others indicates that the deficit is not purely motor but an inability to integrate certain sensory stimuli, with motor output. A similar syndrome of sensory neglect has recently been described in lateral hypothalamic lesioned animals (MARSCHALL *et al.*, 1972). It is obvious that a severe deficit in sensory-motor integration may account for the state of adipsia and aphagia.

The state of akinesia is associated with a state of rigidity which is, e.g. well known in Parkinson's disease. STEG (1964) explained this rigidity as an increased $\alpha$ tonus on the basis of studies after reserpine. We have now studied discharge from ventral roots during spontaneous activity as well as after electrical stimulation of the dorsal roots (STEG and UNGERSTEDT, 1973). Bilaterally DA denervated animals showed increased spontaneous $\alpha$ discharge as well as $\alpha$ reflex discharge. Treatment with apomophine or DOPA in the same doses that abolished akinesia in the behavioural models normalised the $\alpha$ discharge.

Electrical self stimulation is elicited from regions in the brain that anatomically overlap with the ascending DA fibers. In order to test the involvement of DA pathways in the behaviour fifteen unilaterally DA denervated animals were implanted with electrodes bilaterally in the hypothalamus (CHRISTIE *et al.*, 1973). All animals self-stimulated from the electrode on the intact side. Four animals did not self-stimulate on the lesioned side. These four animals showed the highest rotation score on apomorphine and thus the most pronounced supersensitivity which is an indication of the extent of the denervation. The 6-OH-DA injection also damages the NA fibres, however, there was no correlation between failure to self-stimulate and extent of NA degeneration.

A lesion of the nigro-striatal DA pathway may to a varying extent involve the meso-limbic DA pathway. It is difficult to attribute a behavioural effect only to the striatal system. In terms of the rotational behaviour histochemical analysis reveals that the behaviour is elicited even when there is no degeneration of the limbic DA system. Limbic lesions may cause a short period of hypodipsia and hypophagia, while striatal DA degeneration causes the serious syndrome of adipsia and aphagia. Finally the stereotyped behaviour after apomorphine is greatly potentiated by 6-OH-DA induced degeneration of the DA nerve terminals in the nucl. accumbens. The denervation probably induces postsynaptic supersensitivity and the increased stereotyped behaviour may, thus, be due to increased stimulation of DA receptors in this area.

Several authors have argued that DA is involved in stereotyped behaviour while NA is involved in locomotion or exploratory behaviour. In order to quantify different aspects of the drug induced behaviour we designed an automatic "hole-board" where

movements over the bottom of the box as well as the looking into the holes in the bottom were recorded. A normal animal explores the open field as well as the holes. The apomorphine induced behaviour varies considerably with the dose. A low dose of apomorphine (0·1–0·5 mg/kg) causes an interruption of all ongoing behaviour while increased doses induce intense locomotion over the open field with no looking into holes. At still higher doses, sniffing, licking and gnawing develops, while locomotion may decrease. Amphetamine increases locomotion but causes intense looking into holes as well. High doses induce stereotyped behaviour and decreased locomotion similarly to apomorphine. It is tempting to suggest that the apomorphine induced behaviour is an expression of DA receptor stimulation alone, while the amphetamine response is due to a combined increase in DA and NA release. When the effect is confined to DA receptors a series of non-directed patterns of behaviour are triggered. When both NA and DA transmission is increased the motor patterns remain, but they are more directed towards real objects, e.g. the holes.

## NORADRENALINE NEURONS

While degeneration of the DA neurons caused profound and evident changes in behaviour comparable changes after degeneration of the ascending NA axon bundles do not occur. After lesions of the dorsal and ventral NA bundles there are no obvious changes in spontaneous behaviour apart from a slight increase in spontaneous activity in the hole-board. However, when the animals are tested in an operant situation (lever pressing for water reward) several changes may be detected (LJUNGBERG and UNGERSTEDT, 1973). The NA lesioned animals are slower to learn, continue pressing for water longer during a session, and show less extinction if water is removed. However, if the operant testing is discontinued for a longer period and then resumed, the NA lesioned animals show a decreased retention (LJUNGBERG and UNGERSTEDT, 1973).

The behavioural changes are correlated with lesions of the ventral NA bundle innervating the hypothalamus while lesions of the dorsal NA bundle alone do not induce the changes in operant responses. The ventral NA bundle lesion also induces an increased weight gain and moderate overeating (LJUNGBERG and UNGERSTEDT, unpublished). However, the weight increase is not as pronounced as after ventromedial hypothalamic lesions.

Dorsal NA bundle lesions, denervating the cortex and the hippocampus, do not produce evident changes in behaviour *per se*. In a maze task the animals are performing as well as controls. However, after amphetamine (2 mg/kg) the dorsal bundle lesioned animal is unable to run the maze, while the control animal is only slightly impaired. The deficit after dorsal NA bundle lesions seems to be related to an increased stereotyped response to amphetamine (LJUNGBERG and UNGERSTEDT, 1973).

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