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Functional correlates of dopamine neurotransmission

U. UNGERSTEDT and CH. PYCOCK

Knowledge of monoamine neuroanatomy has recently undergone an explosive development. Apart from the wellknown noradrenaline (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT) pathways (Fig. 1) (for references see UNGERSTEDT 1971a) there is now evidence for dopamine pathways to the cerebral cortex (THIERRY et al. 1973, HÖKFELT et al. 1974) and for adrenaline pathways originating in the lower brain stem and sending axons descending into the spinal cord and ascending to diencephalic areas (HÖKFELT et al. 1973). However, our understanding for the functional role played by these pathways is still very primitive. In fact, even our knowledge of the "traditional pathways" is in this respect rather minimal. There are a great number of studies indicating their participation in a vast number of brain functions, e.g. temperature regulation, hormone secretion, blood pressure, sleep-wakefulness, sexual behaviour and so on. However, in most of these instances a detailed knowledge of the functional correlate of monoamine neuron transmission is lacking.

The central dopamine neurons

The major ascending DA pathways originate in the mesencephalon. The cell bodies are localized in the zona compacta of the substantia nigra (group A9) and lateral and dorsal to the interpeduncular nucleus (group A10) (DAHLSTRÖM and FUXE 1964) (Fig. 2). The axons from these cell groups ascend in the medial forebrain bundle. In midhypothalamus they are localized in a dense bundle at the tip of the internal capsule. The axons from group A9 turn laterally through the internal capsule, the globus pallidus and terminate in the nucleus caudatus putamen (from now on referred to as striatum). The axons from group A10 continue rostrally in the medial forebrain bundle to terminate in the olfactory tubercle, the nucleus accumbens and in the septum, i.e. in limbic areas. The relationship between the mesencephalic dopamine neurons and the dopamine nerve terminals in the cortex is so far unknown.

The dopamine system originating in the mesencephalon is reliably associated with functional neurological disorders as Parkinson's disease and it

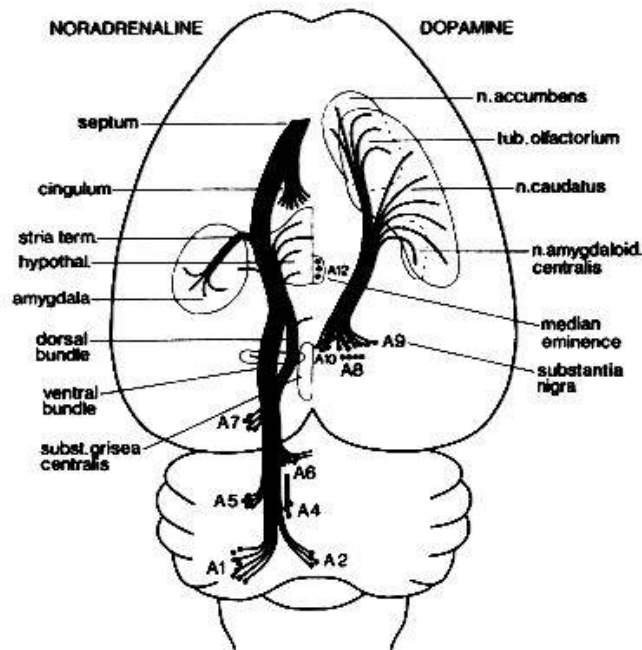


Fig. 1. Horizontal projection of the ascending noradrenaline and dopamine pathways in the rat-brain. The noradrenaline pathways (shown on the left side of the drawing) originate from cell-groups in the lower brain stem (labelled A1–A7). The most caudally localized groups (A1–A2) also send descending axons to the spinal cord (not shown in the picture). The dopamine pathways (shown on the right side of the drawing) originate from cell groups in the mesencephalon (A8–A10). Dopamine cell groups are also localized within the hypothalamus (A12), innervating the median eminence. Apart from the dopamine pathways shown in the picture, there are also dopamine pathways terminating in the cortex; however, their origin is still not known (for references, see text).

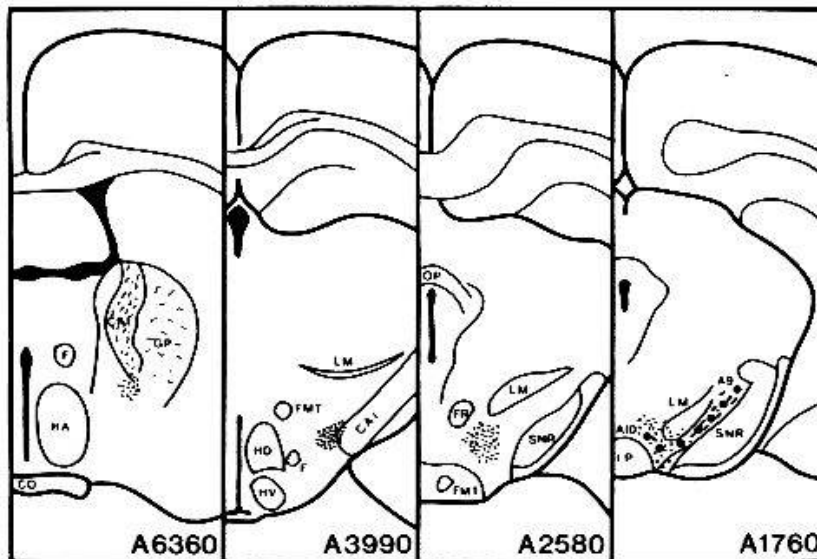


Fig. 2. Major ascending dopamine pathways shown in different frontal sections of the rat brain. The numbers refer to the localization of the frontal section as indicated in the KÖNIG and KLIPPEL stereotaxic atlas. For explanation, see text.

is well established that this disease is associated with a degeneration of the dopamine cell bodies in the substantia nigra (HORNÍKEVICZ 1966).

The discovery that 6-hydroxy dopamine (6-OH-DA) induced a degeneration of peripheral noradrenaline containing neurons (TRANZER and THOENEN 1968) prompted us to try to obtain this degeneration also in the central nervous system. 6-OH-DA was injected stereotaxically into the substantia nigra dopamine cell group (UNGERSTEDT 1968, 1971b, 1974). This treatment induced a degeneration of the entire nigro-striatal dopamine system and a partial degeneration of the more medial mesolimbic dopamine system. When the injection was performed into the ascending dopamine bundle both the striatal and the limbic dopamine nerve terminals degenerated. The lesion seems to be due to a selective uptake of 6-OH-DA into the dopamine neurons. The intra-neuronal oxidation of 6-OH-DA then seems to lesion the neurons from within. This kind of degeneration mechanism will obviously affect mainly those neurons that have the ability to take up and concentrate 6-OH-DA. We have also found that the lesion caused by 6-OH-DA is remarkably specific and superior to conventional lesioning methods of the dopamine neurons (UNGERSTEDT 1968, 1971b; HÖKFELT and UNGERSTEDT 1973). Other authors have reported considerable unspecific damage especially when 6-OH-DA was injected into areas less rich in monoamine nerve terminals (POIRIER et al. 1972). These results are partly explained on the basis of very high concentrations of 6-OH-DA but there also seems to be some variance from laboratory to laboratory in the results obtained with this method. The reason for this has so far not been explained. However, the findings underline the importance of using histological controls when using 6-OH-DA.

Functional changes after unilateral dopamine denervation

A unilateral 6-OH-DA induced degeneration of the ascending DA neurons induces profound functional changes: The rat deviates in movements and posture towards the side of the lesion and often tends to perform actual circulatory movements in this direction. The development of this syndrome is closely associated with the neuronal degeneration as seen in histochemical and electron microscopic studies (Fig. 3). The animal develops its strong tendency to deviate toward the lesioned side within one hour after the 6-OH-DA injection. Beginning about 24 h after the lesion the animal often shows activation and may even start to circle in the opposite direction, i.e. toward the non-operated side. This tendency may last about 10 h. At 48 h the animal is back again in its tendency to deviate toward the lesion and this tendency now remains for the rest of the animal's life. These changes in the motor pattern are closely paralleled by morphological as well as biochemical changes: A lesion of the DA system induces an increase in DA levels. 3 h after a coagulation of the DA axons the biochemically measured dopamine levels in the striatum have actually doubled (ANDÉN et al. 1972; NYBÄCK and SEDVALL 1971). This increase is in all probability due to a de-

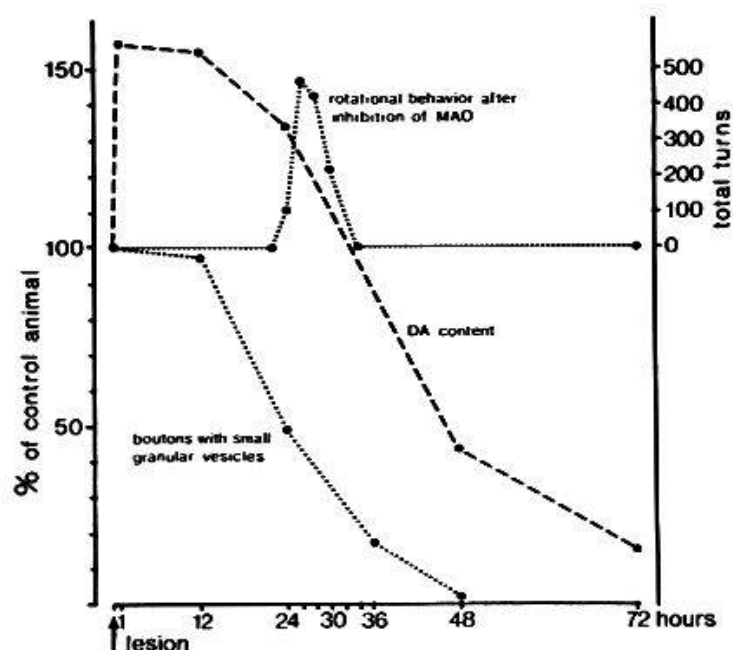


Fig. 3. Degeneration process of the nigro-striatal dopamine system after a lesion of the ascending dopamine pathways. Biochemical studies show an initial rise in the dopamine content of the lesioned neurons. This content decrease at the same time as electron-microscopical studies indicate, a decrease of the number of boutons with small granular vesicles (i.e. a morphological degeneration of the dopamine storage sites within the neuron). The biochemical and morphological degeneration is revealed in functional studies after inhibition of monoamine oxidase: inhibition of this enzyme, inactivating dopamine, permits the dopamine leaving the degenerating nerve-ending to reach the receptor and induce a functional change, in this case rotational behaviour.

crease in nerve impulse dependent DA release, because of the lesion, while synthesis of DA is still going on. About 24 h after the lesion the storage mechanisms are beginning to disintegrate causing a spontaneous release of DA. This causes a shift from hypofunction to hyperfunction in the DA neurons, expressing itself behaviourally as a shift from deviation toward the lesion to the tendency to deviate away from the lesion. After 48 h there is biochemically no DA left and behaviourally the animal is back again in its tendency to deviate toward the lesioned side. Histochemically and in the electron microscope the period between 24 and 48 h is associated with a disappearance of monoamine fluorescence as well as the dense core vesicles detectable in the electron microscope. This decrease is paralleled by an appearance of the degenerating boutons (Fig. 3).

Unilateral removal of the striatum is known to be associated with deviation toward the lesioned side when the DA transmission is increased in the remaining DA system (ANDÉN et al. 1966). The 6-OH-DA lesioned animal is identical to the striatum lesioned animals in so far that it has only one DA system. However, in the 6-OH-DA lesioned animal the post-synaptic cells still remain on the lesioned side, i.e. only the DA afferent neurons have been removed. This type of preparation should be interesting in terms of pre- and postsynaptic acting DA drugs. We therefore constructed a roto-

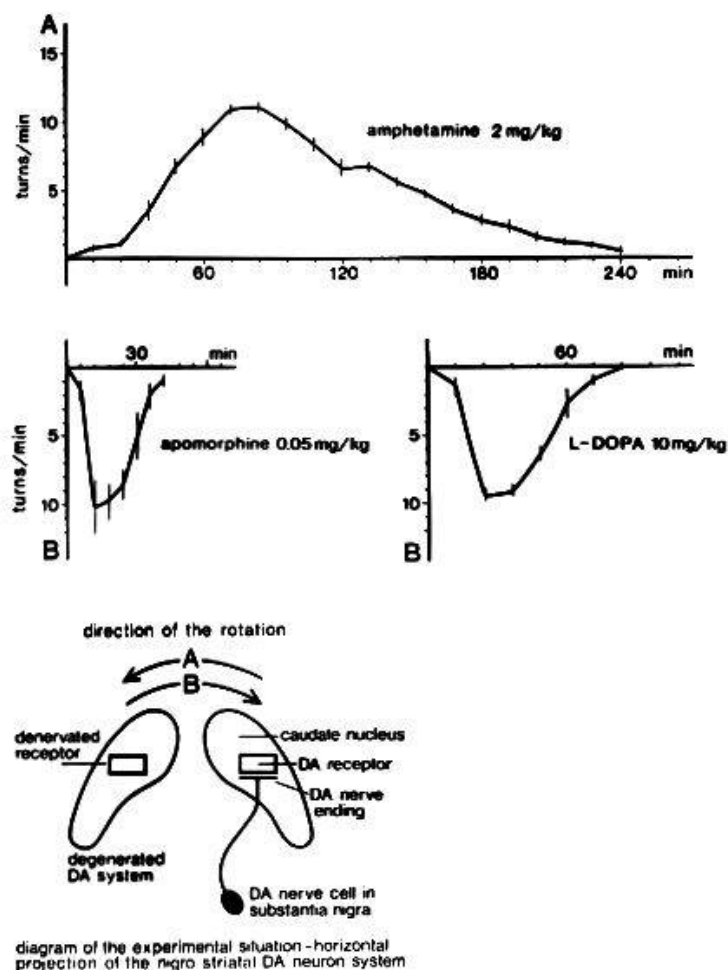


Fig. 4. Rotational behaviour of rats unilaterally denervated with 6-hydroxydopamine. Amphetamine causes release of dopamine from the intact side causing rotation in direction A. Apomorphine preferentially stimulates receptors on the denervated side causing rotation in direction B. L-dopa induces the same effect as apomorphine. Experiments indicate that L-dopa is transformed to dopamine by enzyme remaining on the denervated side. Dopamine is then stimulating the receptor sites.

meter (UNGERSTEDT and ARBUTHNOT 1970) designed to record rotational behaviour (see Fig. 5). In subsequent studies drugs known to release DA were found to increase the motor deviation to the point of actual rotation (UNGERSTEDT 1971d). The animals rotated toward the lesioned side for several hours on e.g. amphetamine (Fig. 4). On the other hand drugs known to stimulate dopamine receptors caused a rotation toward the normal side (UNGERSTEDT 1971c). We explained this as a supersensitivity to dopamine receptor stimulating drugs on the lesioned side as a consequence of the removal of the presynaptic dopamine nerve terminals. In analogy with what is known to occur in the peripheral neuromuscular synaps (LANGER et al. 1967) it may be speculated that the regeneration of the DA nerve terminals induces a postsynaptic supersensitivity to dopamine receptor stimulating agents. In recent electrophysiological studies we (HOFFER et al. 1974, see also FELTZ and DE CHAMPLAIN 1973) have obtained additional support for the existence of a denervation type supersensitivity in the denervated striatum. DA

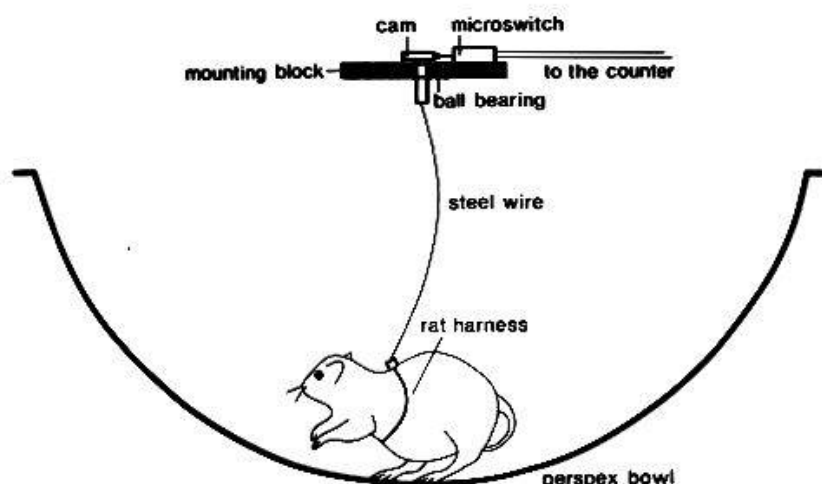


Fig. 5. Schematic diagram of the rotometer. The rat is moving around "freely" within a hemisphere of plexi-glass. The steel-wire transmits its movements to the micro switch arrangement.

and apomorphine were applied microiontophoretically to single cells in the normal as well as 6-OH-DA denervated striatum. The cells were generally inhibited by these drugs, however, the ejection currents necessary to produce threshold inhibition were about 3 times larger on the innervated side as compared to the denervated side (Hoffer et al. 1974). The spontaneous activity in the denervated and the innervated striatum were greatly different (Ljungberg et al., to be published). More cells showed spontaneous firing on the denervated side and the cells fired generally faster than on the innervated side.

In an attempt to find further correlates of dopamine neurotransmission and possibly an explanation to the rotational behaviour we developed a test for sensory function. The test was partly adopted from that described by Marshall et al. (1971). The animal's ability to react to a sensory stimulus was tested by studying its orienting reaction toward the stimulus (Ljungberg and Ungerstedt 1974). Tactile auditory, olfactory and visual stimuli were applied to one side of the body at a time. A normal animal will respond to these stimuli by an orienting reaction toward the stimulus. The unilaterally DA denervated animals showed normal responses on the side of the body ipsilateral to the DA denervation. However, between 3 and 5 days after lesion they showed no orienting reaction when the side contralateral to the lesion was stimulated. After 5 days there was a gradual recovery of certain sensory modalities. They soon regained their ability to react to olfactory stimuli while they never regained their ability to react to tactile stimuli. The fact that the animals at certain points were able to react to one type of sensory stimuli but not to others shows that the deficit was not a motor deficit. The deficit may tentatively be explained as a disruption of sensory motor integration.

The neural connections of the striatum are highly suggestive of a role in sensory motor integration (Nauta and Mahler 1969). The caudate nucleus

receives its main afference in a topographical manner from the cerebral cortex. Its efferent fibers project mainly to the putamen which in turn sends fibres to the thalamus. The thalamo-cortical fibres complete a striato-thalamo-cortical loop that has been regarded as important in performing integrated behavioural activities (BUCHWALD et al. 1961). The nigro-striatal DA pathway supplies about 11% of the total number of boutons in the striatum (HÖKFELT and UNGERSTEDT 1969). These DA nerve terminals are diffusely distributed over the entire striatum. A degeneration of the DA input is known from our electrophysiological studies to cause profound change in the electrical activity of the nucleus (HOFFER et al., to be published). In view of this it is not surprising that any function subserved by the striatum is altered. The further understanding of the mechanism behind the rotational behaviour will probably throw light on the principles behind integration of introceptive as well as extroceptive sensory information with motor output.

Intracranial dialysis of dopamine

The above describes some of our attempts to find anatomical, pharmacological, electrophysiological and behavioural correlates to dopamine function. However, it is obvious that we still lack means of closely following the actual release of the endogenous transmitter in a functional situation. We have therefore attempted to develop a method by which DA may be collected and quantified in the awake unrestrained animal. We will in this paper report a few basic findings related to the methodology as such.

In order to allow both administration and collection of chemical substances from the brain we have utilized the so-called hollow fibres, i.e. dialysis tubes with an outer diameter of about 0.25 mm. These tubes allow molecules with a molecular weight of less than 5000 to pass through their walls. The tubes are inserted through a hole drilled in the temporal bone, passed through the entire brain including the heads of the caudate nuclei and out through the contralateral temporal bone. A Krebs-Ringer solution is passed through the tube with the speed of 0.5–20 μ l/min depending upon the application. The brain DA nerve terminals may be labelled with 3 H-DA by perfusing the isotope solution through the tube. After labelling the release of DA is determined by collecting labelled DA leaving the brain and entering the Krebs solution in the tubing through diffusion. In short, the brain is first labelled with radioactive DA and the release of this DA is studied by perfusing with a medium containing no DA. After the labelling period various treatments may be made aimed at changing the release of DA from DA nerve terminals.

Amphetamine injected intravenously to anaesthetized animals caused a pertinent increase in the efflux of tritium-labelled DA as collected in 15 min fractions and measured by scintillation counting (Fig. 6). An even more prominent increase in dopamine release was found at the end of the experiment when the animal was killed by cervical dislocation. The results demonstrate the usefulness of the intracranial dialysis technique for collecting transmitter release. The method has successfully been tested also in awake freely moving animals (UNGERSTEDT and PYCOCK 1974).

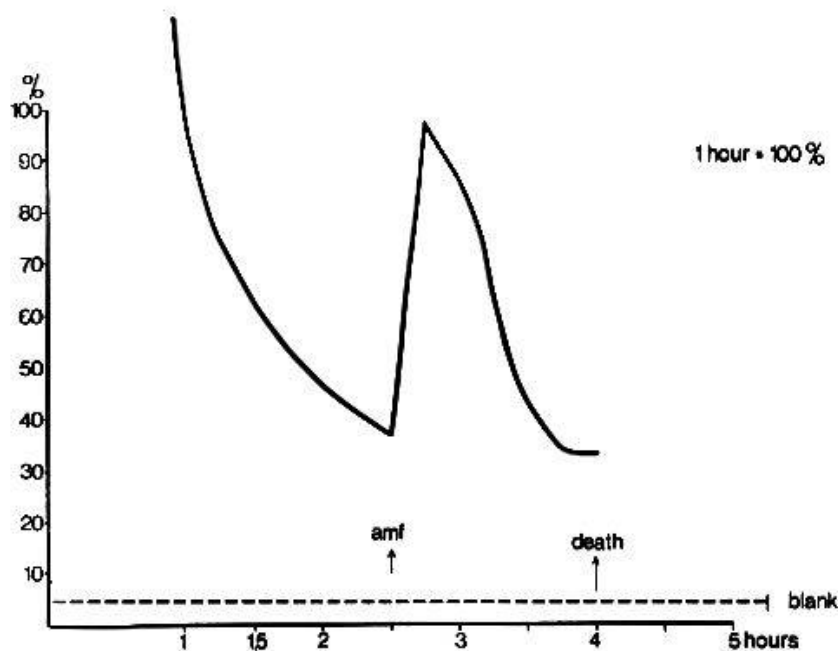


Fig. 6. Tritiated dopamine recovered during the administration of amphetamine (amf). The brain is initially labelled by ^3H -dopamine which is perfused through the hollow fibre. The perfusion is then continued with a Krebs solution and radioactivity recovered. Amphetamine causes a strong increase in the recovered dopamine.

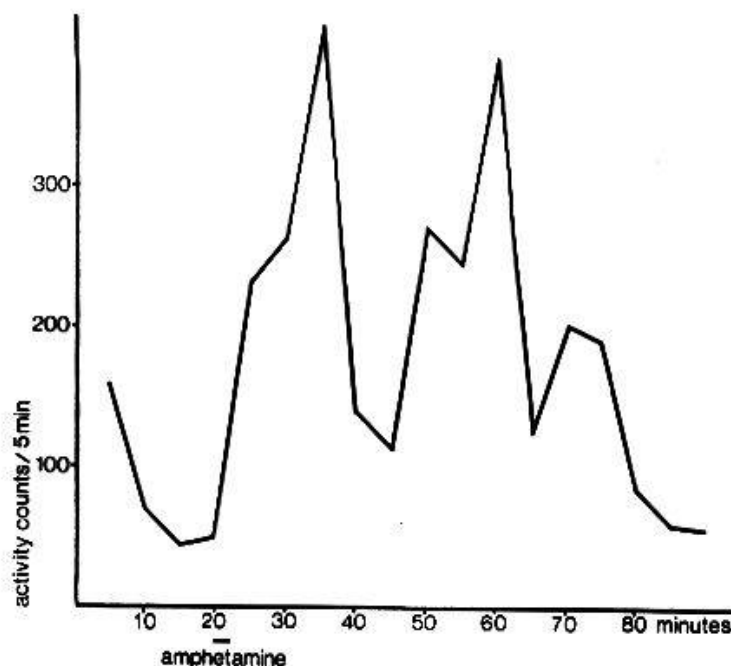


Fig. 7. Activity measured in an activity meter. An amphetamine solution (1 mg/ml) is infused through the fibre as indicated on the diagram. This causes a strong activation of the animal.

The technique also permits administration of chemicals into the brain. Fig. 7 demonstrates such an experiment when amphetamine has been infused into the caudate nuclei through the fibre. The activity of the animal was recorded in an Animex activity meter. The short infusion of amphetamine caused a profound increase in motility.

Our ultimate aim is to increase the sensitivity of the dialysis method to the point when endogenous transmitter release may be studied in the freely moving, behaving animal.

Summary

On the basis of an anatomically highly specific lesion method it has been possible to study the behavioural effects of selective removal of the ascending dopamine neurons in the brain. A unilateral degeneration of the DA neurons induce an asymmetry in movements and posture that may develop into actual circling toward the side of the lesion. This rotational behaviour has been quantified in a rotometer and seems to be a quantitative expression of DA receptor activation. It is possible to follow the course of dopamine nerve degeneration morphologically and biochemically and find a close parallel in the behavioural events as a quantified in the rotometer. In the chronically denervated animal the behavioural studies give evidence for the development of postsynaptic supersensitivity to DA receptor stimulating agents. Subsequent electrophysiological studies have revealed a supersensitivity to microiontophoretically applied dopamine.

A further behavioural correlate to the dopamine degeneration and the resulting change in spontaneous firing frequency in striatal single cells was found in the profound sensory neglect developing contralateral to the lesion. The animal was in fact unable to orient towards any contralaterally applied sensory stimuli in the early phases after the degeneration. This seems well in accordance with the hypothetical involvement of the striatum in sensory motor integration.

In an attempt to include also a biochemical parameter in our functional studies we have developed a method of intracranial dialysis. The method permits administration and recovery of substances to and from the brain, even in the awake freely moving animal. Examples are giving where amphetamine is releasing labelled DA and when amphetamine administered to the brain by dialysis increases the behavioural activity of an animal.

Zusammenfassung

Auf Grund einer hochspezifischen Methode wurden die Verhaltenseffekte nach selektiver Ausschaltung der aszendierenden Dopamin-Neurone im Gehirn untersucht. Die unilaterale Degeneration der Dopamin-Neurone bewirkt eine Asymmetrie von Bewegung und Haltung, welche in eine Wendebewegung übergeht. Dieses Phänomen wurde mit Hilfe eines Rotometers quantitativ erfasst; es scheint quantitativer Ausdruck der Dopaminrezeptor-Aktivierung zu sein. Es ist möglich, den Verlauf der Degeneration der dopaminhaltigen Nerven morphologisch und biochemisch zu verfolgen und eine Korrelation mit den rotometrisch verifizierten Verhaltensänderungen herzustellen. Beim chronisch denervierten Tier ergeben die Verhaltensstudien eine Hypersensibilität der postsynaptischen Membran für Stimulation der Dopa-

minrezeptoren. Elektrophysiologische Untersuchungen zeigen eine Hypersensibilität gegenüber mikroiontophoretisch appliziertem Dopamin.

Ein weiteres Korrelat des Verhaltens zur Degeneration der Dopaminneurone und der daraus resultierenden Veränderung der Spontanaktivität striataler Einzelzellen wurde in einem sehr ausgesprochenen "sensory neglect" gefunden. Dieser "sensory neglect" tritt in der Frühphase der Degeneration auf und betrifft vor allem die Einstellung auf die kontralaterale Umwelt. Diese Beobachtung scheint mit der hypothetisch angenommenen Funktion des Striatums im Rahmen der sensomotorischen Integration gut übereinzustimmen.

Auch ein biochemischer Parameter sollte in unseren Untersuchungen berücksichtigt werden. Aus diesem Grunde wurde die Methode der intrakraniellen Dialyse entwickelt. Diese Methode gestattet die kontrollierte Lokalapplikation von Substanzen auf das Gehirn und deren Wiederfreisetzung beim wachen, freilebenden Tier. Als Beispiel zu diesem Vorgehen wird die durch Amphetamin bedingte Ausschüttung von radioaktivem Dopamin und die damit in Verbindung stehende Zunahme der Spontanaktivität erwähnt.

Résumé

Grâce à une méthode extrêmement spécifique on a pu examiner les effets d'une exclusion sélective des dopamine-neurones ascendants dans le cerveau. La dégénération unilatérale de dopamine-neurones provoque une asymétrie dans les mouvements et la tenue, qui évolue vers une rotation sur soi-même. Ce phénomène a pu être mis en évidence à l'aide d'un rotomètre; il semble être la manifestation quantitative d'une activation des récepteurs de la dopamine. Il est possible de suivre l'évolution de la dégénération morphologique et biochimique de nerfs contenant de la dopamine et de trouver une corrélation avec les altérations de comportement vérifiées par le rotomètre. L'étude du comportement chez l'animal dénervé chronique montre une hypersensibilité de la membrane postsynaptique pour la stimulation des récepteurs de la dopamine. Des études électrophysiologiques montrent une hypersensibilité vis-à-vis de dopamine appliquée par micro-iontophorèse.

On a trouvé une autre relation entre la dégénération de dopamine-neurones et les modifications qui en résultent pour l'activité spontanée de cellules striées, et qui se manifeste par un "sensory neglect" caractérisé. Ce "sensory neglect" apparaît dans les premières phases de la dégénération et atteint surtout le comportement vis-à-vis de l'entourage controlatéral. Cette observation semble bien concorder avec l'hypothèse du rôle du striatum dans l'intégration sensorielle et motrice.

Dans nos recherches nous avons voulu également faire intervenir un paramètre biochimique. C'est dans ce but que fut développée la méthode de la dialyse intracrânienne. Cette méthode permet une application contrôlée de substances sur le cerveau ainsi que leur sécrétion chez l'animal actif et en liberté. A titre d'exemple de cette méthode, l'auteur décrit la libération de

dopamine radioactive sous l'effet de l'amphétamine, qui est en relation avec une augmentation de l'activité spontanée de l'animal.

Riassunto

Grazie ad un metodo che permette di produrre lesioni anatomiche altamente specifiche, è stato possibile studiare gli effetti sul comportamento causati da una rimozione selettiva nel cervello dei neuroni dopaminici ascendenti. La loro degenerazione unilaterale provoca una asimmetria dei movimenti e della posizione, che può accentuarsi in un movimento rotatorio diretto verso la lesione. Questo fenomeno di rotazione è stato apprezzato quantitativamente con un cosiddetto rotometro e sembra essere un'espressione dell'attivazione dei ricettori dopaminici. È possibile seguire morfologicamente e biochimicamente l'evoluzione del processo degenerativo dei rispettivi nervi dopaminici e trovare una correlazione specifica con le turbe del comportamento apprezzate quantitativamente con il rotometro. Nell'animale cronicamente denervato, gli studi del comportamento rivelano lo svilupparsi di una ipersensibilità della membrana postsinattica nei confronti di agenti che stimolano i ricettori dopaminici. Studi elettrofisiologici successivi hanno rivelato una ipersensibilità nei confronti di dopamina applicata con metodo microiontoforetico.

Quale ulteriore fenomeno del comportamento correlato alla degenerazione dei neuroni dopaminici ed alla risultante modificazione dell'attività spontanea di singole cellule del corpo striato, si è constatata una profonda inaccessibilità sensoria che appare nella fase precoce del processo degenerativo, per cui l'animale diventa incapace di orientarsi verso gli stimoli sensori applicati controlateralmente alla lesione. Questo fenomeno sembra ben confermare l'ipotesi di un coinvolgimento del corpo striato nel processo d'integrazione sensomotoria. Al fine di includere anche un parametro biochimico nei nostri studi funzionali, abbiamo sviluppato un metodo di dialisi intracranica. Questo procedimento permette di amministrare e di allontanare delle sostanze dal cervello dell'animale sveglio e che si muove in libertà. Esempi di tale applicazione sono la secrezione di dopamina radioattiva e l'accentuazione dell'attività spontanea dell'animale sotto l'effetto di anfetamina amministrata con la dialisi.

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