Interdependence of the Nigrostriatal Dopaminergic Systems on the Two Sides of the Brain in the Cat

Abstract. *The release of [^{3}H]dopamine in vivo was estimated in the left and right caudate nuclei of the cat during the continuous superfusion of the two structures with* L-*[3,5-^{3}H]tyrosine by means of two "push-pull" cannulas. A lesion made in the left substantia nigra interrupted the release of [^{3}H]dopamine in the ipsilateral caudate nucleus and was associated with a simultaneous increase in the release of [^{3}H]dopamine on the contralateral side. The release of [^{3}H]dopamine also decreased in the left caudate nucleus and increased in the right structure when dopamine was applied to the left substantia nigra which reduces the activity of the left dopaminergic pathway. A total of 120 estimations of the spontaneous release of [^{3}H]dopamine were made simultaneously in the left and right caudate nuclei during periods characterized by a stable physiological state of the animals, and 76 percent of the estimations showed that an increase in the release of [^{3}H]dopamine on one side corresponded to a decrease in the release of [^{3}H]dopamine on the other side, and vice versa. These results demonstrate a close relation between the two nigrostriatal dopaminergic systems.*

Despite numerous studies on the physiology and pharmacology of the nigrostriatal system, little is known about the relations between the dopaminergic pathways on the two sides of the brain, and it has often been assumed that the two anatomically distinct pathways are functionally independent. For example, investigators studying the functions of the dopaminergic pathways or the role of their postsynaptic receptors in animals with a lesion of the dopaminergic system on one side of the brain have assumed that the activity of the contralateral pathway is not affected by the lesion (*1*). Our experiments indicate that there is a close relation between the two nigrostriatal dopaminergic systems: any modification in the activity of one pathway influences the activity of the contralateral pathway.

One way to demonstrate the relation between the two dopaminergic systems is to measure in vivo the simultaneous release of dopamine (DA) in both caudate nuclei. For our experiments we used halothane-anesthetized cats of both sexes or "encéphale isolé" (EI) preparations of cat brains (in which the spinal cord is sectioned at the level of C_1–C_2). "Push-pull" cannulas (made of two concentric tubes) were inserted in each caudate nucleus at the same stereotaxic coordinates (A = 16; L = 5; H = 5) (*2*). L-[3,5-^{3}H]tyrosine, dissolved in an artificial cerebrospinal fluid (CSF) (40 μc/ml) was introduced continuously (500 μl/15 min) through both cannulas, and the release of [^{3}H]DA, selectively formed in dopaminergic terminals, was estimated in the superfusates obtained during successive 15-minute intervals as described (*3*). The [^{3}H]DA released into the superfusates was separated from [^{3}H]tyrosine and ^{3}H-labeled metabolites by ion-exchange chromatography and adsorption on alumina (*4*). The release of [^{3}H]DA was estimated from 105 to 300 minutes after the beginning of the experiments, a period during which a steady state is achieved (Fig. 1) (*3*). To compare the variations in the amount of [^{3}H]DA released from both caudate nuclei (left and right) in different animals, the [^{3}H]DA recovered in each successive fraction was expressed as a percentage of the mean release (100 percent) determined from estimations made in the first five fractions collected (from 105 to 180 minutes) from each side of each animal.

Previous studies indicate that the spontaneous release of [^{3}H]DA depends on nerve activity (*3*). For instance, it is reduced by tetrodotoxin (*3*), which interrupts nerve impulse flow by blocking sodium channels, and is completely abolished by transection of the nigrostriatal dopaminergic pathway (*5*). In our first experiment we examined the effect of the interruption of nerve activity in one dopaminergic pathway on [^{3}H]DA release in the ipsilateral and the contralateral caudate nuclei. A lesion was made in the left substantia nigra by means of a bipolar electrode. As before (*3*), this lesion of the dopaminergic pathway immediately reduced the [^{3}H]DA released in the ipsilateral caudate nucleus. The spontaneous release of the labeled transmitter was decreased by 75 percent 90 minutes after the lesion was made. Furthermore, the release of [^{3}H]DA simultaneously increased in the contralateral (right) caudate nucleus (Fig. 1); this increase, which was probably related to an activation of the dopaminergic neurons, lasted for 45 minutes and reached a peak of 275 percent 30 minutes after the lesion was placed.

Despite the small area affected by the lesion, the placement of which was verified histologically (*2*), other cells besides dopaminergic neurons were destroyed. To reduce the activity of the left dopaminergic pathway more selectively, we introduced DA ($10^{-7}M$) into the left substantia nigra for 1 hour by means of a third push-pull cannula. Previous data had shown that the application of DA in this area reduced the firing of the dopaminergic neurons in the pars compacta (*6*) and reduced the spontaneous release of [^{3}H]DA in the ipsilateral caudate nucleus (*7*). As illustrated in Fig. 2, the release of [^{3}H]DA decreased only during the superfusion of the substantia nigra with DA. The diffusion of DA into surrounding tissues was limited because no decrease occurred when the cannula was not located in the substantia nigra. The modulation of the activity of dopaminergic neurons elicited by DA could be related either to a stimulation of the dopaminergic autoreceptors, as postulated by Aghajanian and Bunney (*6*), or to a DA effect on receptors located on neuronal afferents projecting into the substantia nigra. Indeed, a DA-sensitive adenylate cyclase has been found in this structure (*8–11*), mainly in the pars reticulata (*9, 10*). This adenylate cyclase activity remained in the substantia nigra after the dopaminergic neurons were destroyed by 6-hydroxydopamine (*10, 11*) but was no longer detectable after the destruction of the striato-pallido-nigral connections (*10, 11*).

The selective diminution of nerve firing in the left dopaminergic pathway induced by the nigral application of DA was associated with a concomitant stimulation of [^{3}H]DA release in the contralateral caudate nucleus. This effect was immediate and persisted during the entire superfusion of the left substantia nigra with DA. The introduction of benztropine ($10^{-6}M$) or amphetamine ($10^{-6}M$) into the left substantia nigra resulted in similar opposite effects on [^{3}H]DA release in the left and right caudate nuclei (*12*). We have recently shown that these drugs, which inhibit the reuptake of DA or facilitate the release of the transmitter from dopaminergic terminals, are also able to stimulate in vivo the release of [^{3}H]DA synthesized from L-[3,5-^{3}H]-tyrosine in the cat substantia nigra (*13*). It has been postulated in histochemical and biochemical studies (*14*) that in this structure the transmitter originates from dopaminergic dendrites.

It thus appeared that induced changes in the activity of one dopaminergic pathway were associated with a modification of DA release from the contralateral system. The next step was to investigate whether such effects could occur spontaneously without experimental manipulation of the left dopaminergic pathway.

We measured all the fluctuations in the spontaneous release of [^{3}H]DA in superfusates drawn during successive 15-minute intervals from the left and the right caudate nuclei in 21 EI preparations or halothane-anesthetized cats. Arterial blood pressure, heart rate, alveolar CO_2, and rectal temperatures were monitored continuously, and superfusates were obtained only during long periods when the animals were in a stable physiological state. More precisely, the change in the quantity of [^{3}H]DA released between two successive fractions in the left caudate nucleus was compared to the change simultaneously observed in the right caudate nucleus. In 120 estimations of samples obtained simultaneously from the left and right caudate nuclei, 76 percent showed that fluctuations occurred in opposite directions. An increase in [^{3}H]DA release in one caudate nucleus corresponded to a decreased release of [^{3}H]DA in the contralateral side in the same animal during the same period and vice versa. In 24 percent of the estimations the fluctuations occurred in the same direction, an increase (or decrease) of [^{3}H]DA release on one side being matched by a similar increase (or decrease) on the other side. The amount of [^{3}H]DA released spontaneously varied from one animal to another and even from one caudate nucleus to the contralateral one, but these variations appeared to be related to the location of the cannula within the structure (*3*) and to the awake or anesthetized states of the animals (*3*). The mean values in the spontaneous release of [^{3}H]DA were 2.08 ± 0.31 nc/15 min and 3.10 ± 0.42 nc/15 min in EI preparations (N = 12) and in halothane-anesthetized cats (N = 9), respectively. There were marked differences in the amplitude of the changes in the spontaneous release of [^{3}H]DA between two successive fractions (Fig. 3), and these were partly related to the basal level of the spontaneous release. However, fluctuations that occurred in opposite directions (76 percent) in the left and right caudate nuclei were independent of the amplitude of the changes in ^{3}H[DA] release seen in two successive fractions from each side. This spontaneous balance between the activities of the two dopaminergic systems was observed in 77 percent of the estimations from EI preparations as well as in 75 percent of those from the anesthetized animals despite the differences in the mean level of the spontaneous release of DA in the two groups.

Our experiments demonstrate a relation between the two dopaminergic systems. This phenomenon can be compared to an observation of Hull *et al.* (*15*) who detected in the cat and monkey an increase in the activity of some cells in the left caudate nucleus after a homolateral lesion was made in the medial forebrain bundle which interrupted the nigrostriatal dopaminergic pathway. This effect was associated with a simultaneous reduction in the firing rate of cells located in the contralateral caudate

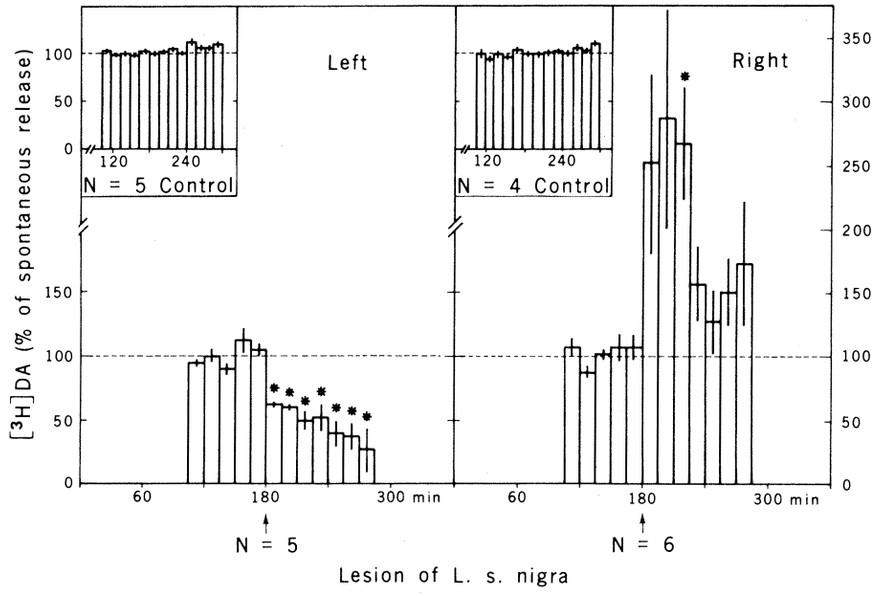

Fig. 1. Effects of lesions of the left substantia nigra (*L.s. nigra*) on the release of [^{3}H]DA in the left and right caudate nuclei in EI preparations of cats. A bipolar electrode was implanted into the left substantia nigra (A = 3.5; L = 3; H = −4). Then, L-[3.5-^{3}H]tyrosine (20 μc/500 μl) dissolved in an artificial CSF was introduced at a rate of 500 μl/15 min into two push-pull cannulas inserted in both structures and [^{3}H]DA was estimated in successive 15-minute fractions. The lesion was made 180 minutes after the beginning of the experiments by means of a direct current (5 ma, 15 seconds). The spontaneous release of [^{3}H]DA in the left and right caudate nuclei in control experiments is indicated in the upper parts of each panel. The [^{3}H]DA released in each fraction was expressed as the percentage of the mean spontaneous release estimated between 105 and 180 minutes after the beginning of the experiment (that is, superfusion) in each cat. Results are means ± standard error of N experiments. Asterisk indicates $P < .05$ when compared to [^{3}H]DA release in the corresponding fractions of the control experiments.

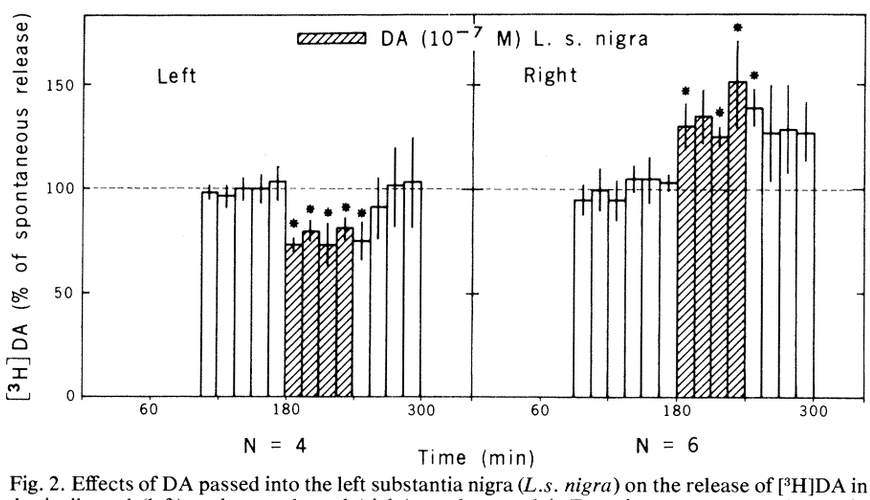

Fig. 2. Effects of DA passed into the left substantia nigra (*L.s. nigra*) on the release of [^{3}H]DA in the ipsilateral (left) and contralateral (right) caudate nuclei. Experiments were conducted in halothane-anesthetized cats. The release of [^{3}H]DA in the two caudate nuclei was estimated as described in Fig. 1. A third push-pull cannula was used to superfuse continuously the substantia nigra with an artificial CSF. Dopamine ($10^{-7}M$) was introduced into the CSF during 1 hour from 180 to 240 minutes after the beginning of the experiments. Results were expressed as indicated in Fig. 1 (means ± standard error of N experiments). Asterisk indicates $P < .05$ when compared to [^{3}H]DA release in the corresponding fractions of the control experiments (see upper parts of the panels of Fig. 1). No differences were found in the spontaneous release of [^{3}H]DA in the left and right sides in control experiments in which animals were implanted with an electrode or a third cannula in the left substantia nigra.

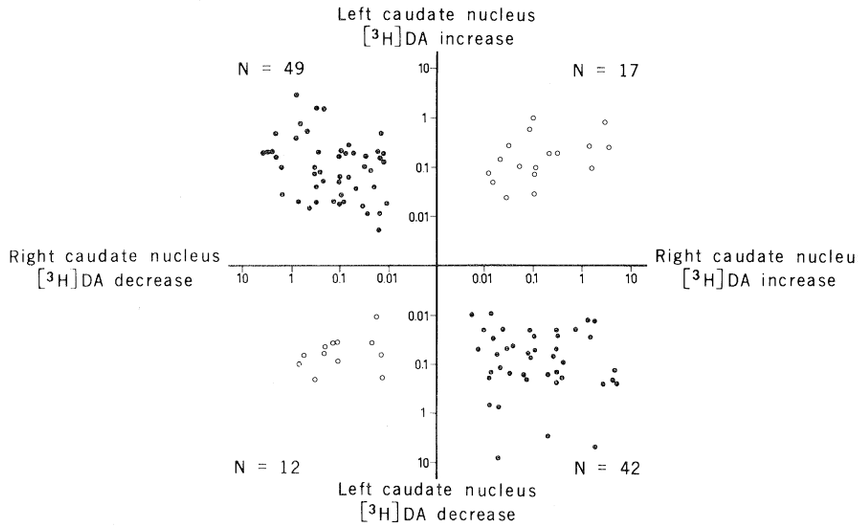

Fig. 3. Simultaneous changes in the spontaneous release of [^{3}H]DA in the right and left caudate nuclei of 21 EI preparations (N = 12) or halothane-anesthetized cats (N = 9). The change corresponding to the difference in the quantity of [^{3}H]DA released between two successive 15-minute fractions measured in the left caudate nucleus ([^{3}H]DA increase or [^{3}H]DA decrease) was compared to the change that occurred simultaneously in the right caudate nucleus. We made 120 estimations of these variations during periods when arterial blood pressure, heart rate, alveolar CO_2, and rectal temperature remained stable. Each open and solid circle represents a change in [^{3}H]DA release (nanocuries per 15 minutes) occurring simultaneously in the left (vertical axis) and in the right (horizontal axis) caudate nuclei. The solid circles correspond to cases (N = 91) in which the release of [^{3}H]DA was simultaneously increased in one side and decreased in the contralateral side. The open circles correspond to the cases (N = 29) in which the release of [^{3}H]DA was simultaneously increased (or decreased) in both sides. This distribution differed significantly from a homogenous distribution according to the χ^2 test ($P < .001$).

nucleus. Moreover, this balance between the activity of the cells of the two structures was observed not only shortly after the lesion was made but also several weeks later in monkeys with permanently implanted electrodes.

There is no evidence for a direct anatomical connection between the two substantia nigra which could explain the reciprocal control of the activities of the two dopaminergic systems. However, the nucleus ventralis lateralis of the thalamus receives important inputs from the striatum through the homolateral globus pallidus and substantia nigra (*16*) and sends projections to the ipsilateral cerebral motor cortex (*17*) which may control both caudate nuclei (*18*). Since DA is released from dopaminergic dendrites in the substantia nigra (*13*), and since this dendritic release is modulated in physiological states (*19*), the nigrothalamic pathway could be influenced by DA which is released from dendrites in the pars reticulata. The connection between one cerebral cortex and the contralateral striatum could thus be the final pathway by which fluctuations in the activity of the dopaminergic system induce simultaneous variations in the activity of the contralateral dopaminergic pathway. Indeed, the contralateral cortical projection could influence the dopaminergic system directly in the striatum or at the substantia nigra level through the striatonigral γ-aminobutyric acid pathways or substance P connections (*20*). A direct effect of the contralateral cortical projection on dopaminergic terminals within the striatum cannot be excluded since the release of DA can be presynaptically controlled by transmitters other than DA which are also contained in the striatum (*21*). Alternatively, since each cerebral motor cortex receives direct input from both substantia nigrae (*22*), this could be another way (excluding the thalamus) by which a striatum could be in connection with the contralateral substantia nigra through the cortico-striatal projection.

Our data indicate that biochemical, pharmacological, and behavioral events observed after a unilateral lesion has been made in a dopaminergic system should be interpreted with caution. The relation between the two dopaminergic pathways, which might be of physiological significance in the coordination of posture and movements, could be helpful in understanding the pathology of the extrapyramidal system.

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