

REVIEW ARTICLE

Dendritic release of dopamine in the substantia nigra

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Dopamine can be released in the substantia nigra from the dendrites of nigrostriatal dopaminergic neurones, to be involved there in the self-regulation of the dopaminergic cells, to control the release of neurotransmitters from nigral afferent fibres and to influence the activity of nigral non-dopaminergic cells.

IT is still widely considered that the transfer of information is unidirectional in neurones which communicate through chemical synapses. Messages travelling from dendrites, through somata and down axons finally reach the nerve terminals from which the neurotransmitter is released. By interacting with postsynaptic receptors located on somata or dendrites, the neurotransmitter will then modify the activity of the target neurones. Several years ago, however, it was suggested that molecules could also be released from dendrites to influence surrounding cells or nerve terminals¹⁻⁵. In this article, we review the accumulating evidence which indicates that dopamine (DA) is released from dendrites of the nigro-striatal dopaminergic neurones and contributes to the processing of signals in the substantia nigra (SN). Complementary anatomical, electrophysiological and biochemical studies show that DA is released from dendrites to regulate not only the release of neurotransmitters from some nigral afferent fibres, but also the activity of the dopaminergic neurones and of other nigral efferent neuronal pathways. Consequently, by acting in the striatum and the SN, the dopaminergic neurones may influence the messages delivered to the striatum by the cortico- and thalamo-striatal fibres and those emerging from the SN through projections innervating the thalamus and the pontine nuclei.

Substantia nigra as a site for study of dendritic release of DA

Nigro-striatal dopaminergic neurones are particularly well suited to the study of neurotransmitter release from dendrites in the central nervous system. Their cell bodies are mainly concentrated in the pars compacta and their long, ramified and varicose dendrites extend throughout the pars reticulata of the SN¹. Their fibres, in contrast to those of non-dopaminergic cells of the pars reticulata, do not emit collaterals within the SN⁶. Intraventricular or locally injected radioactive catecholamines readily label the cell bodies and the dendrites of the dopaminergic neurones whilst showing the virtual absence of catecholaminergic nerve terminals⁷⁻¹⁰. Furthermore, few if any nigral boutons degenerate after intraventricular or nigral injections of 6-hydroxydopamine^{11,12}, a neurotoxin which selectively destroys catecholaminergic fibres. The SN is also an appropriate site for the study of the dendritic release of DA because there is good evidence not only that DA can be synthesized¹³⁻¹⁸ and stored^{1,10,19,20,21,22} in dopaminergic dendrites, but that it can also be inactivated. However, it should be noted that the mechanism of DA re-uptake in dendrites may differ from that in nerve terminals¹. Furthermore, little is yet known about the mechanisms of DA storage in dendrites. Although a few large or small dense core vesicles are seen to be

scattered in some thin distal dendrites using 5-hydroxydopamine as a marker of monoamine storage sites²³, no specialized vesicles are seen in dopaminergic dendrites identified by the autoradiographic method^{7,10}. It has been suggested that DA is stored in smooth endoplasmic reticulum^{10,17,22}.

DA metabolism in the SN

A guide to the metabolism of DA is commonly provided by measurement of its metabolites, methoxytyramine (3-MT), dihydroxyphenylacetic (DOPAC) and homovanillic (HVA) acids. This approach has also been applied to the rat SN to investigate DA metabolism in dendrites in various experimental conditions and to compare the results with those obtained in the striatum.

Korf *et al.*^{24,25} observed an enhanced accumulation of DOPAC and HVA not only in the striatum but also in the SN shortly after the electrical stimulation of the middle forebrain bundle through which dopaminergic fibres run towards the striatum. The changes in the levels of nigral DA metabolites led

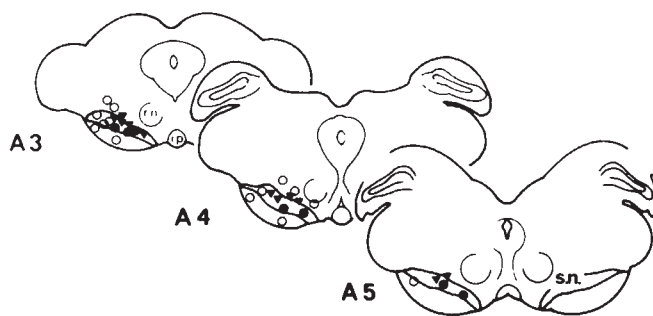


Fig. 1 *In vivo* spontaneous release of newly formed ³H-DA in the cat SN. Halothane anaesthetized cats were implanted with a push-pull cannula in the left. ³H-tyrosine (50 Ci mmol⁻¹, 50 μCi ml⁻¹) was delivered continuously in the push-pull cannula (2 ml h⁻¹) and ³H-DA was estimated in 10-min superfusate fractions 1 h after onset of superfusion, at a time when the spontaneous release of the ³H-transmitter reached a steady state. In each case, the mean spontaneous release of ³H-DA was estimated on the basis of results obtained in five successive fractions and the localization of the tip of the push-pull cannula was determined. The spontaneous release of ³H-DA was much higher when the tip of the cannula was in the SN (●, > 0.5 nCi per 10 min; ▲, 0.1–0.5 nCi per 10 min) than when it was in the lateral part or outside of the SN (○, < 0.1 nCi per 10 min). A3, A4, A5: frontal planes of the stereotaxic atlas of Smidea and Nicmek; r.n., red nucleus; i.p., interpeduncular nucleus; s.n., substantia nigra

Table 1 Release of dopamine from substantia nigra slices (S) or dendrosomes (D)

Treatment			Effect	Blocked by:	Refs
(S)(1)	K ⁺	2.4 × 10 ⁻² M	+	Ca ²⁺ -free medium or high-Mg ²⁺ medium	21
(S)(1)(2)	<i>d</i> -Amphetamine	10 ⁻⁵ M	+		37
(S)(3)	K ⁺	4.7 × 10 ⁻² M	+		10
(S)(1)	<i>d</i> -Amphetamine	10 ⁻⁵ M	+		38
(S)(1)	GABA (K ⁺ -evoked release)	10 ⁻⁴ M	+	Picrotoxin	38
(D)(3)	<i>d</i> -Amphetamine	10 ⁻⁴ M	+		35
(S)(1)	Substance P	10 ⁻⁵ M	+		39
(S)(1)	K ⁺	5.0 × 10 ⁻² M	+	Ca ²⁺ -free medium	40
(S)(1)	Glycine	10 ⁻⁴ M	+	Strychnine	40
(D)(1)	Substance P*	10 ⁻⁸ M	+		36
(S)(1)	GABA*	10 ⁻⁵ M	-		36
(S)(1)	Veratridine	3.0 × 10 ⁻⁶ M	+	Tetrodotoxin	33

(1), Preloaded with exogenous ³H-DA; (2), endogenously synthesized ³H-DA; (3), endogenous. +, Increased; -, decreased.

* Derived from estimation of tissue ³H-DA levels.

them to suggest that DA was released from dendrites as a result of antidromic activation of the dopaminergic neurones.

Various drugs acutely influence the nigral DA metabolism, sometimes in a manner different from that in the striatum. For example, amphetamine reduces DOPAC formation in both structures whilst increasing 3-MT levels only in the striatum²⁶, whereas reserpine, which depletes striatal and nigral levels of DA²⁷, increases the levels of DOPAC and 3-MT in the striatum, but not in the SN²⁶⁻²⁸. In addition, γ -hydroxybutyrate, a general anaesthetic which enhances striatal DA levels and synthesis, induces opposite effects in the SN^{29,30}. These and other^{27,28,31,32} discrepancies also indicate that changes in nigral DA metabolism reflect events occurring in dendrites and not in axon collaterals.

Dendritic release of DA *in vitro*

Using slices of the rat SN, Geffen *et al.*²¹ demonstrated a calcium-dependent release of ³H-DA from dendrites with potassium depolarization. Similar observations were made with slices of pars compacta or pars reticulata or by measuring the release of endogenous DA¹⁰. A veratridine-evoked release of ³H-DA sensitive to tetrodotoxin was also shown, indicating that dopaminergic dendrites have fast sodium channels³³ (Table 1). Gentle homogenization of nigral dopaminergic dendrites can produce particles which behave like synaptosomes on density gradient centrifugation^{34,35}. These dendrosomes take up ³H-DA which can be released by potassium depolarization³⁶ (Table 1). Amphetamine, a potent releasing agent of DA from nerve terminals, stimulated the release of DA from SN slices or

dendrosomes^{35,37,38} (Table 1). Other studies indicated that transmitters present in large amounts in the SN could also influence the dendritic release of DA (Table 1). γ -aminobutyric acid (GABA), which did not affect the spontaneous release of ³H-DA newly taken up from SN slices, potentiated the potassium-induced release of the ³H-amine and this effect was blocked by picrotoxin³⁸. Substance P³⁹ and glycine^{40,41} stimulated spontaneous efflux of ³H-DA from rat nigral slices, the latter effect being antagonized by strychnine⁴⁰ (Table 1).

Dendritic release of DA *in vivo*

Our method for demonstrating the *in vivo* dendritic release of DA makes use of a push-pull cannula to superfuse continuously the SN of halothane-anaesthetized cats with a physiological medium containing ³H-tyrosine, the precursor of ³H-DA⁴². This method ensures specificity because tyrosine hydroxylase is only located in dopaminergic neurones in the SN. In fact, ³H-DA represented >90% of the total content of ³H-catecholamines recovered in superfusates. Furthermore, the spontaneous release of ³H-DA was only substantial when the push-pull cannula was within the SN (Fig. 1). ³H-DA release was reduced in the absence of calcium and markedly increased during a pulse application of potassium. Tetrodotoxin, which reduces the spontaneous release of ³H-DA from nerve terminals in the caudate nucleus, induced the opposite effect when applied in the SN⁴². This effect excludes a nigral release of ³H-DA from nerve terminals and suggests that some nigral afferent fibres inhibit the spontaneous dendritic release of DA. Furthermore, the inability of tetrodotoxin to reduce the spontaneous release of ³H-DA from dendrites could indicate that fast sodium

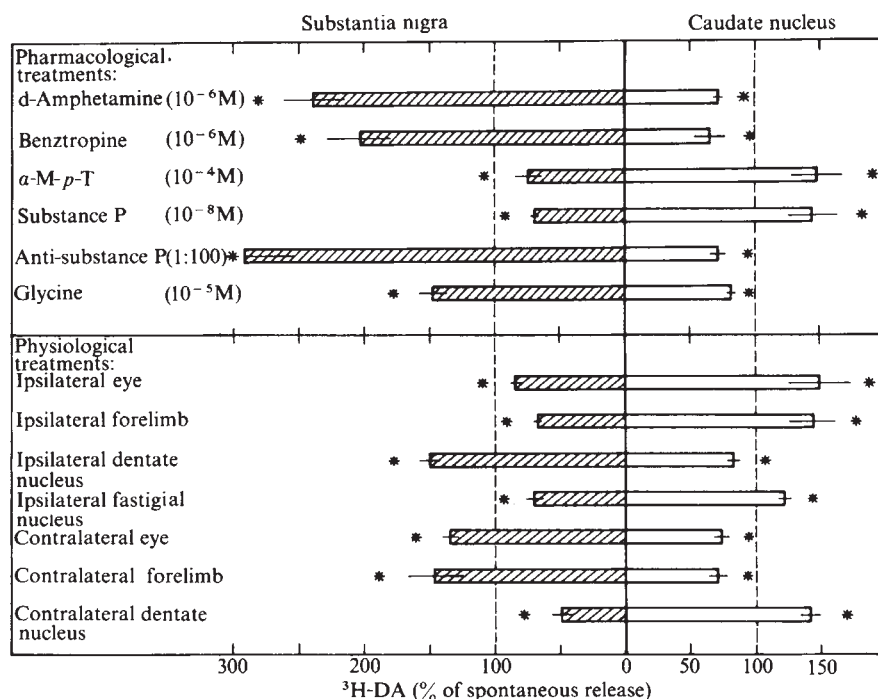
Table 2 Remote induced changes in ³H-DA release in both substantia nigrae (SN) of the cat

Treatment	Left SN	Right SN	Refs
<i>d</i> -Amphetamine in left caudate nucleus	129.1 ± 8.4*	108.6 ± 10.8	51
<i>d</i> -Amphetamine in left SN	—	63.7 ± 12.5*	51
α -M- <i>p</i> -T in left caudate nucleus	63.9 ± 8.3*	105.9 ± 7.3	51
α -M- <i>p</i> -T in left SN	—	119.3 ± 7.0	51
Diazepam in left SN	—	80.6 ± 5.7*	
K ⁺ in left SN	—	160.8 ± 40.3*	52
Light flashes in right eye	134.3 ± 6.2*	84.6 ± 5.1*	53
Electrical stimulation of right forelimb	146.5 ± 21.0*	66.7 ± 3.3*	53
Electrical stimulation of left motor cortex	199.0 ± 37.1*	Not estimated	49
Electrical stimulation of left visual cortex	157.1 ± 17.0*	Not estimated	49
Electrical stimulation of right dentate nucleus	49.3 ± 7.8*	150.2 ± 8.4*	50
Electrical stimulation of right fastigial nucleus	79.1 ± 5.9	69.6 ± 7.7*	50

Experiments were performed in cats implanted with push-pull cannulae as described in Fig. 2 legend. Changes in ³H-DA release are expressed as per cent of the mean spontaneous release estimated during the hour preceding the treatments. They were estimated during the first 10-min (amphetamine, potassium) or the third 10-min (other cases) fraction after the start of treatment, and are the mean of data obtained with groups of 4-7 animals compared with results from untreated cats. Data corresponding to the local effects are not indicated (—). Drug treatments: *d*-amphetamine (10⁻⁶ M); α -M-*p*-T (α -methylparatyrosine, 10⁻⁴ M); diazepam (10⁻⁵ M); K⁺ (potassium, 30 mM).

* $P \leq 0.05$ using Student's *t*-test.

Fig. 2 Examples of treatments which induced opposite changes in the release of ^3H -DA from dendrites in the SN and from nerve terminals in the ipsilateral caudate nucleus. The effects of the unilateral nigral application of dopaminergic drugs, substances affecting substance P transmission, glycine or unilateral physiological stimuli on the release of newly formed ^3H -DA in the SN and the corresponding caudate nucleus were examined in halothane-anaesthetized cats implanted with push-pull cannulae. ^3H -DA was estimated in successive 10-min fractions during the continuous delivery of ^3H -tyrosine to each cannula. *d*-Amphetamine, benzotropine, α -M-*p*-T, substance P, substance P antibody or glycine were introduced for 10–60 min into the superfusing medium delivered to the SN 3 h after the start of the experiments. The physiological stimuli comprised the delivery of light flashes applied for 10 min to the ipsilateral or contralateral eye, the electrical stimulation of the ipsilateral or contralateral forelimb (10 min), the electrical stimulation of the ipsilateral or contralateral dentate nuclei of the cerebellum (10 min) or the ipsilateral cerebellar fastigial nucleus (10 min). The results are expressed as per cent of the mean spontaneous release of ^3H -DA estimated during the hour preceding the treatments and correspond to changes observed during the first 10-min application of amphetamine, benzotropine and glycine, or during the third 10-min fraction after the start of application of other treatments. They are the mean of data obtained with groups of 3–7 animals, compared with results from untreated cats. Statistical analysis was done using Student's *t*-test; *, $P \leq 0.05$.



channels are not involved in this process, in contrast to that observed in the caudate nucleus. In fact, dendritic spikes resistant to the neurotoxin have already been described^{43–45}.

Several neurotransmitters present in the SN influence the dendritic release of ^3H -DA. A stimulation of ^3H -DA release was induced by glycine (Fig. 2), acetylcholine and serotonin but substance P induced the opposite effect^{46,47} (Fig. 2). Although GABA was ineffective, the GABA agonist muscimol enhanced the dendritic release of ^3H -DA⁴⁸ whereas the reverse was seen with diazepam, a benzodiazepine known to facilitate GABAergic transmission.

One critical step in our *in vivo* studies has been the demonstration that changes in the activity of neurones with functional connections to the SN, or involved in sensory motor processes, affected the dendritic release of DA. Thus, ^3H -DA release was altered by electrical stimulation of the motor or visual cortices⁴⁹ (Table 2) and of the fastigial and dentate cerebellar nuclei⁵⁰ (Table 2, Fig. 2), as well as by local pharmacological interruption, or facilitation of dopaminergic transmission in the ipsilateral caudate nucleus or in the contralateral SN⁵¹ (Table 2, Fig. 3). Further evidence that messages originating in one SN could influence the dendritic release of DA in the contralateral structure came from the local nigral application of potassium⁵² or diazepam (Table 2). Marked changes in the dendritic release of ^3H -DA were also induced by delivery of sensory stimuli⁵³ (Table 2, Fig. 2). Sometimes, the changes in ^3H -DA release remained for up to 1 h after treatment, suggesting the involvement of long-term regulatory processes which have still to be elucidated. These *in vivo* experiments indicate that the dendritic release of DA from the nigro-striatal dopaminergic neurones is a physiological event which must contribute to the local transfer of information.

Dendritic DA can influence the activity of ipsilateral dopaminergic neurones

Several years ago, Bunney and Aghajanian⁵⁴ suggested the presence of dopaminergic receptors on dopaminergic cell bodies or dendrites in the rat SN. They observed that the microiontophoretic application of DA or of apomorphine reduced the

firing rate of the dopaminergic cells and that this effect was prevented or reversed by neuroleptics⁵⁵. Groves *et al.*⁵⁶ reported that amphetamine (a drug which releases DA) inhibited the firing rate of pars compacta neurones after its local application and that this effect was prevented by peripheral injection of α -methylparatyrosine⁵⁷, the inhibitor of catecholamine synthesis. Because these authors also observed that the local application of haloperidol enhanced the firing rate of pars compacta neurones, they suggested that DA could be released from dendrites and was involved in a self- or lateral-inhibition of the nigral dopaminergic neurones⁵⁶. The presence of dopaminergic autoreceptors in the rat SN has since been confirmed by binding studies with labelled spiroperidol^{58–60} or apomorphine⁶¹ after selective degeneration of the dopaminergic neurones.

To confirm the changes in the firing rate of dopaminergic cells seen in electrophysiological studies, we have measured changes in DA release from nerve terminals during pharmacological modification of the nigral dopaminergic transmission. The nigral application of DA by a push-pull cannula reduced the spontaneous release of ^3H -DA in the ipsilateral caudate nucleus of the cat⁶² and similar results were obtained when the dendritic release of ^3H -DA was enhanced by the local application of amphetamine or benzotropine⁶³ (Fig. 2). Conversely, the release of ^3H -DA increased in the caudate nucleus during the nigral application of α -methylparatyrosine⁵¹ (Figs 2, 3) or of dopaminergic blockers⁶³, indicating that DA released from dendrites tonically inhibits the activity of the nigral dopaminergic cells. Opposite changes in the dendritic release of ^3H -DA and the release of the ^3H -transmitter from nerve terminals were also seen during modifications of glycinergic and substance P-ergic transmission in the SN (Fig. 2). The simplest hypothesis is that DA released from dendrites exerts its inhibitory effect through dopaminergic autoreceptors situated on dopaminergic cell bodies or dendrites.

We have also obtained evidence to support earlier biochemical^{64,65} and electrophysiological⁶⁶ data consistent with the hypothesis of a neuronal feedback loop involved in the control of the activity of the nigro-striatal dopaminergic neurones⁶⁷. Thus, when amphetamine was applied to the caudate nucleus, it not only increased local dopaminergic transmission, but also

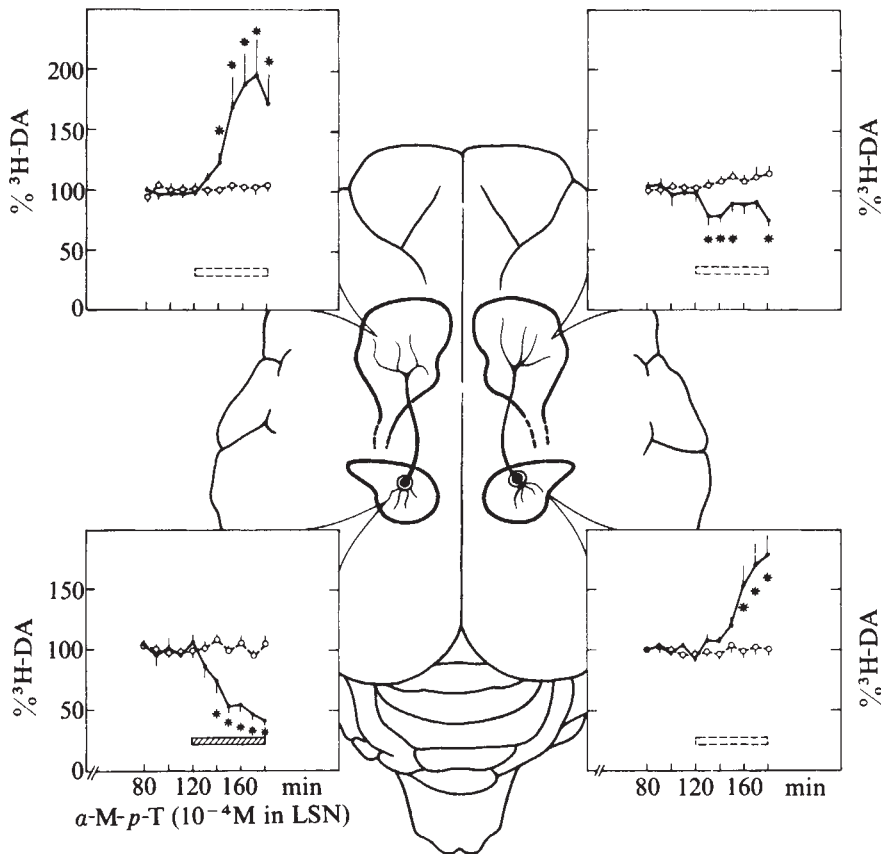


Fig. 3 Effects of α -M-*p*-T application into the left SN on the release of ^3H -DA from the two caudate nuclei and the two SN. Four push-pull cannulae were simultaneously implanted in halothane-anaesthetized cats to measure the release of ^3H -DA formed from ^3H -tyrosine ($50 \mu\text{Ci ml}^{-1}$) in both SNs and both caudate nuclei. α -M-*p*-T was introduced for 60 min into the artificial cerebrospinal fluid superfusing the left SN (LSN) (hatched bar). In each animal and for each cannula, ^3H -DA in each successive fraction was expressed as per cent of an average spontaneous release calculated from the five fractions collected before treatment. Data are the mean \pm s.e.m. of results obtained with five animals (\bullet). *, $P \leq 0.05$ when compared with corresponding control values obtained in five untreated animals (\circ).

stimulated the dendritic release of ^3H -DA in the SN; α -methylparatyrosine induced the opposite effects⁵¹ (Table 2). Therefore any changes in the dopaminergic transmission in the caudate nucleus may in turn affect the activity of the nigral dopaminergic cells through the influence of striato-nigral fibres on dopaminergic dendrites. The identity of the neurones involved in the activation or the inhibition of the dopaminergic cells has yet to be conclusively determined although substance P neurones may be responsible for activation^{46,47,62,68} (Fig. 2) and GABA neurones for inhibition^{69,70}.

Because the modulation of the activity of dopaminergic cells by nigral afferent neurones can be mediated by their influence on the dendritic release of DA, a decreased release of DA from SN dendrites accompanied by an increased release of DA from nerve terminals in the ipsilateral caudate nucleus, and vice versa, should also be observed in physiological conditions. This pattern of responses was observed after unilateral electrical stimulation of the dentate or fastigial cerebellar nuclei⁵⁰, which send monosynaptic projections to the SN, or with the unilateral delivery of visual or somatic stimuli⁵³ (Fig. 2). It is not yet known whether inhibitory signals mediated by DA release from dendrites are always involved in the regulation of the activity of the dopaminergic neurones.

It will also be important to establish how DA reaches the dopaminergic autoreceptors located on parent or other dopaminergic neurones in the SN. Are there functional dendrodendritic synapses²² or appositions¹⁰ as suggested by some authors or are the dendrites always separated by glial elements connected by multiple gap junctions as claimed by other workers⁷¹? The latter features could subserve a modulatory role of DA in the SN which would explain the long-term changes in activity of the dopaminergic neurones seen in several of our *in vivo* experiments.

Dendritic DA can control nigral afferent and efferent pathways

The presence of dopaminergic receptors on nigral afferent fibres and on non-dopaminergic efferent neurones already suggests a

role for dendritic DA in the presynaptic regulation of the release of other nigral neurotransmitters or in the control of the activity of non-dopaminergic cells. That postsynaptic dopaminergic receptors are associated with nigral afferent fibres is shown in the rat by the unchanged nigral DA-sensitive adenylate cyclase activity after degeneration of the nigral dopaminergic cells compared with the decrease after destruction of striato-nigral neurones⁷²⁻⁷⁴.

As ^3H -spiroperidol binding sites not coupled to the DA-sensitive adenylate cyclase are still detectable after destruction of the dopaminergic cells, some dopaminergic receptors also seem to be located on non-dopaminergic cells in the SN⁵⁸⁻⁶⁰. In fact, cells in the pars reticulata have been shown to be sensitive to the microiontophoretic application of DA⁷⁵. More recently, Ruffieux and Schulz⁷⁶ have observed that ~40% of the pars reticulata cells were excited by DA in the rat and that this effect was antagonized by fluphenazine. Furthermore, half of these cells identified by antidromic activation corresponded to the nigro-thalamic neurones. It is thus highly probable that numerous nigral non-dopaminergic neurones can be influenced by DA released from the dendrites of the dopaminergic neurones—this is also supported by recent autoradiographic studies which indicate that both apomorphine⁷⁷ and amphetamine⁷⁸ enhance glucose utilization in the pars reticulata of the SN and that the apomorphine effect is reversed by neuroleptics.

Reubi *et al.*⁷⁹ obtained the first evidence for a role of DA in the presynaptic regulation of a neurotransmitter release from nigral afferent fibres when they observed that DA and amphetamine stimulated the release of ^3H -GABA previously taken up in slices of the rat SN, and that these effects were blocked by neuroleptics. More recently, Van der Heyden *et al.*⁸⁰ have obtained comparable results *in vivo* although GABA release was either enhanced or decreased depending on the concentration of DA or apomorphine used. These results suggest that dopaminergic receptors coupled to the DA-sensitive adenylate cyclase are located on GABA striato-nigral fibres. In contrast, the striato-nigral substance P afferent fibres seem to lack dopaminergic receptors because the release of

substance P from rat SN slices was not influenced by DA or dopaminergic agonists⁸¹.

A series of experiments in which we investigated the mechanisms involved in the reciprocal regulation of the two nigro-striatal dopaminergic pathways demonstrated that DA released from dendrites influences the activity of non-dopaminergic nigral cells. Cats implanted with one push-pull cannula in each SN and caudate nucleus allowed us to investigate the effects of unilateral nigral facilitation or interruption of dopaminergic transmission not only on the activity of the ipsilateral dopaminergic neurones but also on the release of DA from terminals and dendrites of the contralateral dopaminergic neurones. Amphetamine, which when applied to one SN facilitated the local release of ³H-DA and reduced the ³H-transmitter release in the ipsilateral caudate nucleus (Fig. 2)^{51,63}, induced opposite effects in the contralateral SN (decreasing ³H-DA release) (Table 2) and caudate nucleus (increasing ³H-DA release)⁵¹. The unilateral nigral application of α -methylparatyrosine produced the opposite results (Fig. 3) and other experiments revealed that these contralateral effects were mediated by DA released from dendrites but not from terminals of the ipsilateral dopaminergic neurones⁵¹. Thus DA released from dendrites in one SN influences non-dopaminergic nigral cells involved in the regulation of the activity of the contralateral dopaminergic neurones. As no direct connections have been described between the two SN, a polysynaptic neuronal loop projecting to the contralateral SN must be involved. The nigro-thalamic neurones which can be excited by DA⁷⁶ could contribute to this neuronal loop. In fact, the contralateral effects induced by amphetamine or α -methylparatyrosine are suppressed after lesion of the thalamic massa intermedia⁸². The nigro-thalamic neurones are not the only ones to be influenced by dendritic DA—indirect evidence suggests that this is also the case for the nigral neurones projecting to the dorsal raphe. Indeed, in cats implanted with push-pull cannulae, the application of DA or α -methylparatyrosine in one SN induced changes in serotonin release in both caudate nuclei, which could reflect modifications of the activity of dorsal raphe serotonergic neurones⁸³. These results emphasize the role of dendritic DA in the control of signals leaving the SN through non-dopaminergic cells.

Unfortunately, there is as yet no firm morphological evidence for the dendro-axonic synapses suggested by biochemical data which indicate that dendritic DA is involved in the regulation of transmitter release from some nigral afferent fibres. However, Reubi and Sandri⁷¹ have observed large special symmetrical junctions in the pars reticulata between dendrites and axons and Hattori *et al.*¹⁷ have suggested that dendro-axonic transmission occurs in some axo-dendritic synapses in which vesicle-like structures are seen to be attached to the post-synaptic membrane. However, some of the dendro-dendritic synapses²² or appositions¹⁰ observed in the pars reticulata could correspond to sites by which dendritic DA influences non-dopaminergic nigral cells, as indicated by electrophysiological and biochemical studies.

Conclusions

Our knowledge concerning nigral dopaminergic transmission is now as broad as that acquired for dopaminergic transmission intervening at the level of nerve terminals in the striatum. The dendrites of the nigro-striatal dopaminergic neurones have the capacity to synthesize, store and release DA. However, the dendrites seem to differ from the nerve terminals as they contain very few vesicles and the smooth endoplasmic reticulum seems to be the storage site of the transmitter; furthermore, it is very unlikely that fast sodium channels are to be involved in the dendritic release process occurring in physiological states. Several neuronal pathways which project to the SN influence directly or indirectly, through local microcircuits, the release of DA from dendrites. As shown in Fig. 4, by acting on various types of dopaminergic receptors, only some of which are coupled to a DA-sensitive adenylate cyclase, DA released from

dendrites exerts several functions. One of the most paradoxical effects of the dendritic DA is to inhibit tonically the activity of the nigro-striatal dopaminergic neurones by self- or lateral-inhibition; dopaminergic autoreceptors are involved in this phenomenon (Fig. 4:1). There is already some evidence that DA released from dendrites regulates the presynaptic release of GABA from terminals of the striato-nigral GABAergic neurones; dopaminergic receptors associated with a DA-sensitive adenylate cyclase mediate this effect (Fig. 4:2). Other dopaminergic receptors are located on some nigral neurones mainly distributed in the pars reticulata of the SN; these non-dopaminergic neurones could be interneurones involved in microcircuits (Fig. 4:3) or nigral efferent neurones (Fig. 4:3). We already know that DA exerts an excitatory effect on the nigro-thalamic neurones which contribute to a polysynaptic neuronal loop by which dendritic DA in one SN influences the activity of the contralateral nigro-striatal dopaminergic neurones. As contact between dopaminergic dendrites and glial cells⁷¹ and capillaries¹⁰ have been described (Fig. 4:4), the role of the dendritic DA may not be restricted to the transfer of information between neurones.

Further morphological studies at the electronmicroscopic level are required to define more precisely the relationships between dopaminergic dendrites and target cells. It also remains to be established whether or not DA released from dendrites acts at a distance from its release sites. Present biochemical techniques do not permit the monitoring of the *in vivo* release of transmitters on a time scale familiar to electrophysiologists. Therefore, the role of the dendritic release of DA during fast changes in activity of the nigral dopaminergic cells is not yet known. However, we already know that the changes in the dendritic release of DA are generally of long duration, even when they are induced by physiological treatments such as sensory stimuli. Such a phenomenon explains the prolonged modification of the activity of the dopaminergic cells observed in several situations. This time dimension is another peculiar feature of the signals mediated by dendritic DA and provides further evidence for a modulatory role of the nigro-striatal dopaminergic neurones in the transfer of information in the SN and the striatum.

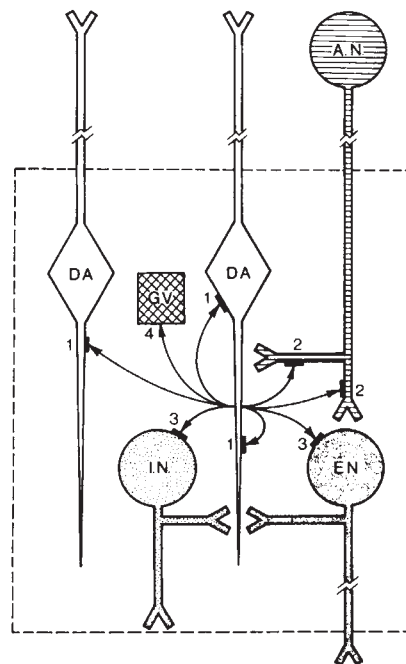


Fig. 4 Schematic representation of the various sites of action of DA in the SN: (1) dopaminergic autoreceptors; (2) dopaminergic receptors located on nerve terminals of striatonigral pathways (AN, afferent neurones); (3) dopaminergic receptors which could be located on nigral interneurones (IN) or on nigral non-dopaminergic efferent neurones (EN); (4) interactions with glial or vascular elements (GV).

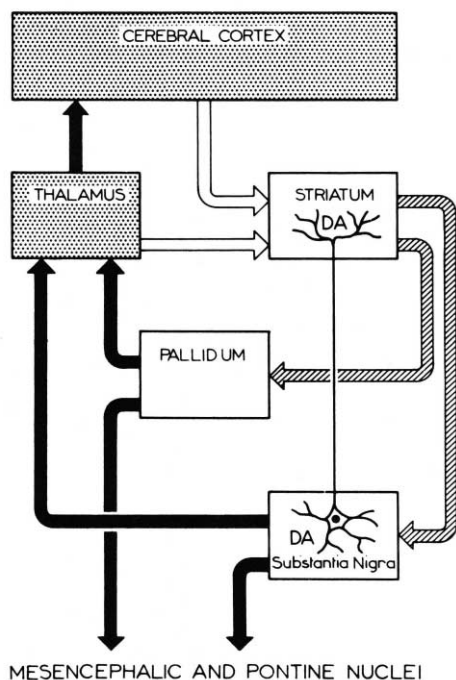


Fig. 5 Schematic diagram of some extrapyramidal circuits illustrating the role of nigro-striatal dopaminergic neurones in filtering messages travelling through the striatum and the substantia nigra. Open arrows: main inputs to the striatum; hatched arrows: main outputs from the striatum; black arrows: main outputs from the basal ganglia. DA: release of dopamine from nerve terminals and dendrites of the nigro-striatal dopaminergic neurones.

Shepherd's proposal that a single neurone consists of several functional units⁵ may apply to the nigro-striatal dopaminergic neurones which display functional properties both in the striatum and the SN (Fig. 5). Thus, at one level, DA released from the terminals of these nerves contributes to the filtering of messages delivered to the striatum by various afferent fibres, including the cortico- and thalamo-striatal fibres, and by influencing the activity of large populations of striatal cells it modulates the transit of signals converging on the pallidum and the pars reticulata of the SN. At another level, DA released dendritically within the SN is involved in the processing of information passing through the nigral pars reticulata in the direction of the thalamus, the subthalamic nucleus and various mesencephalic or pontine nuclei. It is thus not surprising that the nigro-striatal dopaminergic neurones have a critical role in the coordination of sensory motor processes.

One important question is to determine whether or not all central neurones share the capacity to release their transmitter from dendrites. In most cases, studies similar to those carried out on the dendrites of the nigro-striatal dopaminergic neurones are impaired by the co-existence of dendrites, nerve collaterals or nerve terminals of the same type of neurones in a given brain nucleus. However, it has already been suggested that GABA could be released from dendrites in the olfactory bulb⁸⁴, and DA released from amacrine cells in the retina⁸⁵ could originate from dendrites because this type of interneurone has no axon. Using sophisticated electrophysiological analysis, dendro-dendritic excitatory and inhibitory synapses have been particularly investigated in the olfactory bulb⁵. Furthermore, synaptic circuits through dendrites have now been found in several brain areas including the retina, the cerebral cortex, the basal ganglia, the thalamus and the suprachiasmatic and trigeminal nuclei⁵. Therefore, there is little doubt that the chemical transfer of information through dendrites is not a feature unique to the nigro-striatal dopaminergic neurones.

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