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Organization of Central Nervous System Dopaminergic Pathways

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With 2 Figures

Summary

In the present paper the organization of central nervous system dopaminergic pathways is concisely reviewed. Six dopaminergic systems are described: the midbrain efferent system, the tubero-infundibular, the diencephalo-spinal, the incerto-hypothalamic, the periventricular, and the retinal systems. Anatomo-functional correlations can be presently outlined for most dopamine-containing networks, and anatomo-clinical studies indicate that they are globally affected in patients suffering from Parkinson's disease.

Introduction

Largely due to the development of new and sensitive morphological techniques, knowledge on the organization of central nervous system dopaminergic pathways has rapidly grown during the second half of this century. Following the pioneering efforts of Falck *et al.* (1962), the first cytochemical demonstration of catecholamine-containing neurons was obtained in the 1960s (Dahlström and Fuxe, 1964; Fuxe, 1965): methodological limitations did not allow, at that time, to differentiate dopamine- from the other catecholamine-containing neurons. More than twenty years later, our current knowledge stems from a wealth of interdisciplinary data, which have confirmed and expanded the earlier observations. The number of

histological techniques, which are available for studying neural connections, has also grown consistently over the last twenty years. Anterograde and retrograde degeneration techniques in most cases have been replaced by tract-tracing methods based on the use of radiolabeled compounds, horseradish peroxidase, or fluorescent dyes (see: Heimer and Robards, 1981). These new techniques have also been used (alone or in combination with cytochemical demonstration of transmitters) for studying the histological organization of chemically identified neurons (Cuénod and Streit, 1983; Descarries and Beaudet, 1983; Hökfelt *et al.*, 1983). Data obtained by means of cytochemical and histological techniques will be reviewed in the present paper, which is aimed at presenting a condensed picture of the organization of dopamine systems in the brain. For more detailed morphologic and comparative data the reader is referred to a recently published volume (Björklund and Hökfelt, 1984).

Dopamine pathways are non-diffuse, topographically organized, anatomical tracts, originating from dopamine-containing neurons, which are grouped in different brain regions. The dopamine-containing cell groups were identified in early histofluorescence studies by means of logograms, a histochemical terminology first introduced by Dahlström and Fuxe (1964) and later supplemented by Björklund and Nobin (1973). The histochemical descriptions of A 9, A 10, and A 12 groups tallies with classic anatomical terminology, as these dopamine-containing regions respectively correspond to pars compacta of the substantia nigra, to the ventral tegmental area, and to arcuate nucleus of the hypothalamus. The remainder of dopaminergic cell clusters are located within one or more anatomical structures. Group A 8 is located in the lateral midbrain tegmentum, in a region corresponding to the caudal part of substantia nigra (often referred to as retrorubral area). Groups A 11 and A 14 are located in the diencephalon, in close proximity to the third ventricle: group A 11 lies in the caudal thalamus and in the contiguous dorsal hypothalamus, and group A 14 is situated in the rostral hypothalamus. Cell group A 13 is located in the zona incerta and in Forel's H 1 field. Finally, dopaminergic cells located in the olfactory bulb and in the retina have been denominated groups A 16 and A 17, respectively (see Hökfelt *et al.*, 1984). Neural pathways originating from dopamine-containing cell groups constitute seven main projection systems, which are listed in Table 1.

Table 1. *Dopaminergic pathways in the central nervous system*

System	Origin	Targets
Midbrain efferent	Retrorubral area (A 8)	Caudate nucleus, nucleus accumbens
	Substantia nigra (A 9)[1]	Caudate nucleus, putamen, globus pallidus, nucleus accumbens, olfactory bulb, cerebral cortex (see text) locus coeruleus
	Ventral tegmental area (A 10)[2]	Caudate nucleus, putamen, nucleus accumbens, olfactory bulb, cerebral cortex (see text), hippocampus, amygdala, lateral habenular nucleus, locus coeruleus
Tubero-infundibular	Arcuate and periventricular hypothalamic nuclei (A 12, A 14)	Median eminence, intermediate and posterior lobes of the pituitary
Diencephalospinal	Dorsal and posterior hypothalamus (A 11)	Intermedio-lateral cell columns of spinal cord
Incerto-hypothalamic	Zona incerta, posterior hypothalamus (A 11, A 13)	Hypothalamus, lateral septum
Periventricular	Mesencephalic and diencephalic periaqueductal and periventricular gray (A 11, A 14)	Periaqueductal and periventricular gray, thalamus, hypothalamus
Olfactory bulb	Periglomerular cells (A 16)	Olfactory glomeruli
Retinal	Inner nuclear layer (A 17)	Inner and outer plexiform layers

[1] Main subset is the nigro-striatal pathway.
[2] Main subsets are the mesencephalo-limbic and mesencephalo-cortical pathways.

Midbrain Efferent System

The midbrain dopamine-containing cell groups (A 8, A 9, and A 10) give rise to a complex array of efferent pathways, most of which are bound rostrally to reach various forebrain regions (Fig. 1). The variety of terminal fields impinged upon by midbrain dopamine neurons supports the view that different anatomical subsets may constitute individual functional entities (e.g., see: Glowinski *et al.*, 1984). Contrastingly, some other argument supports the belief that midbrain dopamine neurons belong to a unique anatomical system. First, since no boundaries exist between the substantia nigra, ventral tegmental area, and retrorubral area, neurons located in these structures constitute a continuous cell system (Fallon and Moore, 1978; Moore and Bloom, 1978; Poirier *et al.*, 1983) (Fig. 2). Second, the vast majority of ascending midbrain efferent fibers course through a single anatomical tract, the medial forebrain bundle, from which they branch off to their terminal fields (see Moore and Bloom, 1978). Finally, putative subsets of the midbrain efferent system cannot be clearly differentiated on the basis of their hodological organization, because: (1) efferent projections of the three midbrain dopamine-containing cell groups partially overlap, and (2) within each cell group perikarya projecting to different target sites are largely intermixed (see below). Taking these considerations into account, the midbrain efferent system can be schematically regarded as a complex anatomical entity, connected to a large number of different target sites, taking origin chiefly from two midbrain nuclei, the substantia nigra and the ventral tegmental area.

Identified projection sites of nigral dopamine-containing neurons include the neo- and paleo-striatum (nucleus caudatus, putamen, globus pallidus, nucleus accumbens), the olfactory bulb and olfactory nuclei, the piriform, and perirhinal and pregenual frontal cortices, the amygdala, the subthalamic nucleus and the locus coeruleus (see references in: Lindvall and Björklund, 1978 b, 1983; Moore and Bloom, 1978). The projection to neostriatum, which constitutes the nigro-striatal pathway, is by far the most important nigral efferent system (Lindvall and Björklund, 1978 a). This pathway is, in fact, a mesencephalo-striatal tract, containing minor projections arising from the A 8 and A 10 cell groups (Albanese and Minciacchi, 1983; Beckstead *et al.*, 1979; Simon *et al.*, 1979; Ungerstedt, 1971; van der Kooy, 1979),

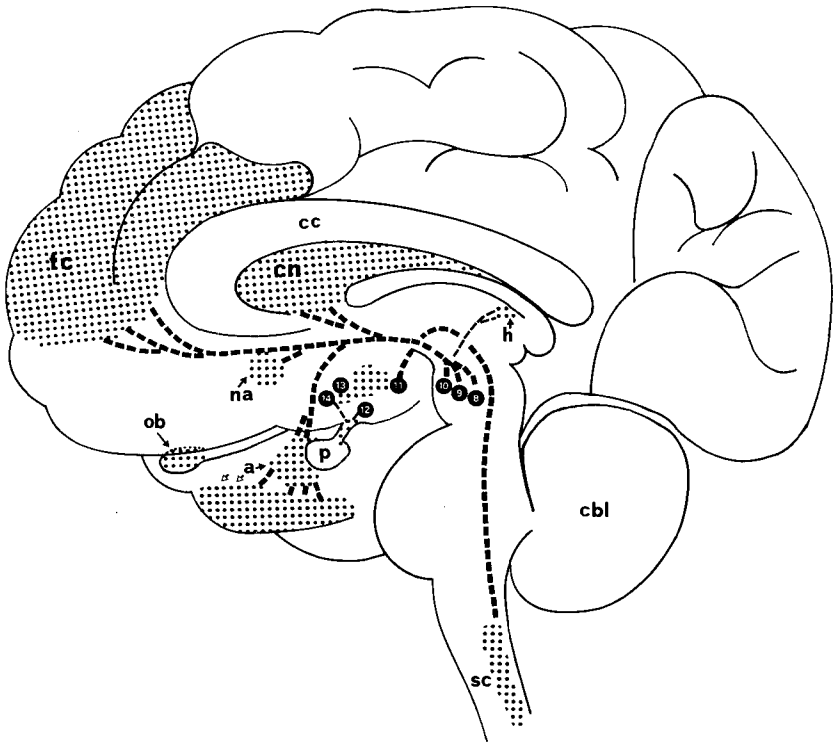


Fig. 1. Schematic representation of the organization of main dopamine neuron systems, as seen on a mid-sagittal projection of the human brain. The topography of dopamine-containing cell groups is represented by numbered black spots; broken lines indicate the distribution of dopamine-containing fibers; dotted areas represent the main terminal sites of dopaminergic pathways. Information condensed on this schematic drawing is not exhaustive (see text for further information). For reasons of clarity, the combining from *mesencephalo-* (which seems more proper than prefix *meso-*) has been used in combination with different suffixes to indicate any of the midbrain efferent pathways. Abbreviations: *a* amygdala (solid arrow) and peri-amygdaloid limbic cortex (open arrows); *cbl* cerebellum; *cc* corpus callosum; *cn* caudate nucleus; *fc* frontal cortex; *h* habenula; *na* nucleus accumbens; *ob* olfactory bulb; *sc* spinal cord; *8–14*, A 8–A 14 dopamine cell groups

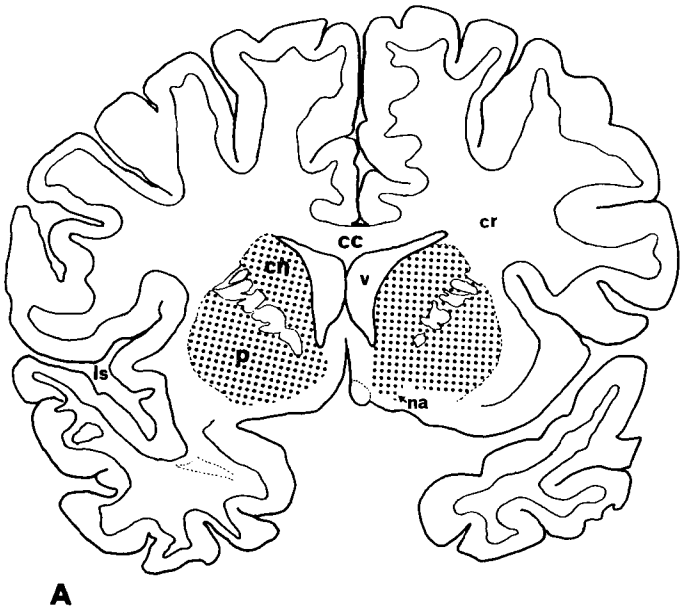
which distributes richly to the entire neostriatum (Fallon and Moore, 1978). In addition, some collateral branches of nigrostriatal axons end up in the globus pallidus, where they constitute diffuse and sparse plexus of dopamine-containing terminals (Lindvall and Björklund, 1979). The anatomical organization of nigral efferent projections

depends, as well as that of other midbrain efferent pathways, upon two distinct (and, to some extent, opposite) principles (see: Moore, 1982; Moore and Bloom, 1978): first, midbrain efferent neurons give rise to a highly collateralized and rich terminal arborization (e.g., as in the neostriatum, or in the frontal cortex, etc.); second, they appear to share with the other dopamine-containing systems a topographically organized pattern of projections. This contrast probably explains why several different topographic principles have been so far proposed for the mesencephalo-striatal tract, none of which has been still conclusively accepted (see review in Lindvall and Björklund, 1983).

Ascending efferent projections from the ventral tegmental area reach quite a few forebrain territories, including the lateral habenular nucleus, the nucleus accumbens, the neostriatum, the olfactory tubercle, the lateral septal nucleus, the amygdala, the hippocampus, and the piriform, entorhinal, suprarhinal, and pregenual cortices (see references in: Lindvall and Björklund, 1978 b, 1983; Moore and Bloom, 1978). Descending projections from the ventral midbrain tegmentum have been studied less extensively: midbrain dopamine-containing neurons located in the substantia nigra and ventral tegmental area have been shown to project bilaterally to the locus coeruleus (Swanson, 1982), while other putative dopaminergic descending projections still need further confirmation (see: Lindvall and Björklund, 1983). Due to the richness in different projection sites arising from neurons located in the ventral tegmental area, understanding their functional role is quite complex. The term *mesolimbic* was introduced by Ungerstedt (1971) to indicate pathways originating from the midbrain dopamine-containing neurons (largely located in the ventral tegmental area), and terminating upon limbic forebrain regions. Subsequent discovery of the dopaminergic mesencephalo-cortical projection (Berger *et al.*, 1974; Lindvall *et al.*, 1974 a) led to propose a tripartite picture of the organization of ventral tegmental area efferent projections. Certainly, when considering the functional role played by the midbrain efferent system it can be assumed that different physiopathological competences pertain to neurons connected with cortical, limbico-rhinencephalic, or striatal regions. This view is also supported by studies using multiple retrograde tract-tracing techniques (Swanson, 1982; Albanese and Minciacchi, 1983), which have shown that, in spite of a rich terminal arborization within projection nuclei (e.g., see above), pathways belonging to the midbrain efferent system give off very few collateral

branches to separate target regions. The pattern of collateralization is only a little richer among territories belonging to the same anatomo-functional group (Albanese and Minciacchi, 1983). This implies that each individual midbrain dopaminergic neuron has a highly preferential projection site. Interestingly, the organization of mesencephalo-cortical projections has been recently re-evaluated: it seems now that dopaminergic terminals are present in several cortical regions, including motor and visual areas (Berger *et al.*, 1985; Törk and Turner, 1981).

Several studies using different experimental approaches have highlighted the existence of biochemical heterogeneities in the midbrain efferent neurons (for references, see: Lindvall and Björklund, 1983). It has been shown, in fact, that dopamine-containing neurons located in the substantia nigra and ventral tegmental area are intermixed with non-dopaminergic perikarya, and that both dopaminergic and non-dopaminergic somata project to the same target territories. Consequently, it can be assumed that most, if not all, pathways of the midbrain efferent system are chemically heterogeneous: it has been calculated, in fact, that non-dopaminergic neurons account for about 5% of the total population of mesencephalo-striatal perikarya (van der Kooy *et al.*, 1981), and for approximately 10–15% of mesencephalo-cortical neurons (Albanese and Bentivoglio, 1982). It is likely that pathways arising from ventral tegmental area contain more non-dopaminergic fibers than those originating from substantia nigra, as nigral neurons are densely packed in the pars compacta, and loose neuronal texture of the ventral tegmental area favours more complex cytochemical arrangements (see, also, Poirier *et al.*, 1983). Biochemical heterogeneity, however, must not be regarded as a unique feature of catecholamine-containing pathways, for a similar organization has been also shown to occur in cholinergic systems (Albanese *et al.*, 1985). The chemical nature of non-dopaminergic neurons of the midbrain efferent system is still poorly understood: in fact, while no "classic" neurotransmitter has been identified for these neurons, Hökfelt and coworkers (see review in: Hökfelt *et al.*, 1984) have shown that the neuropeptides cholecystokinin and neurotensin are contained within some dopaminergic and non-dopaminergic neurons of the ventral midbrain tegmentum; it is not presently clear whether these or other neuropeptides may act as primary transmitters for the non-dopaminergic neurons (see, also: Albanese and Altavista, 1984).



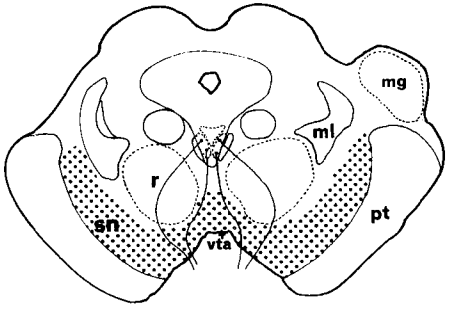


Fig. 2. Drawings obtained from two coronal sections of the human brain schematically representing the distribution of dopaminergic terminal sites in the neostriatum and nucleus accumbens (*A*), and the topography of dopamine-containing perikarya located in the substantia nigra and in the ventral tegmental area (*B*). Section A has been drawn from a coronal section passing through the optic chiasma (not shown); section B is a transverse section of the rostral midbrain passing through the superior colliculus and the red nucleus. Abbreviations: *cc* corpus callosum; *cn* caudate nucleus; *cr* corona radiata; *mg* medial geniculate body; *ml* medial lemniscus; *na* nucleus accumbens; *p* putamen; *pt* pyramidal tract; *r* red nucleus; *sn* substantia nigra; *v* lateral ventricle; *vta* ventral tegmental area

Tubero-infundibular Neurons

Tubero-infundibular dopaminergic neurons originate from the periventricular and arcuate hypothalamic nuclei: in the periventricular nucleus, dopamine-containing perikarya (group A 14) are irregularly scattered among non-dopaminergic neurons; in the arcuate nucleus, they constitute a distinct and well-defined neuronal grouping (A 12). The hodology of tubero-infundibular neurons is highly topographical (Björklund *et al.*, 1973). Ventrally bound axons reach the median eminence, the infundibular stem, and the intermediate and neural lobes of pituitary (see review in: Lindvall and Björklund, 1978 a). In the median eminence, where the primary plexus of hypophyseal portal circulation is located, dopamine-containing terminals end up in close contact with the plexus capillaries (Ajika and Hökfelt, 1973). The main functional role of tubero-infundibular dopaminergic neurons is the inhibition of prolactin secretion from pituitary: dopamine released in the blood stream acts directly upon receptors of the D 2 type, which are located on the adenohypophyseal, acidophil, prolactin-secreting cells (see: Kebabian *et al.*, 1984; Reichlin, 1981). Possible specific functional differences between tubero-infundibular dopaminergic neurons located in the A 12 and A 14 groups have not been described yet; in addition, their physiological activities are dependent upon interaction with other monoaminergic and peptidergic systems (see: Reichlin, 1981).

Diencephalo-spinal Neurons

The most important descending dopaminergic system has been identified quite recently (Björklund and Skagerberg, 1979; Blessing and Chalmers, 1979; Hökfelt *et al.*, 1979). Neurons of origin are located in the caudal diencephalic A 11 group, and possibly also in cell group A 13. Axons course through the brain stem to reach the spinal cord, where they terminate at all levels in the dorsal horns, and, particularly, in the intermedio-lateral cell columns (Skagerberg *et al.*, 1982) around preganglionic sympathetic neurons (Dahlström and Fuxe, 1965). This organization suggests that the diencephalo-spinal neurons may play a role in controlling the spinal cord sympathetic nervous system.

Incerto-hypothalamic and Periventricular Systems

Incerto-hypothalamic dopamine neurons have been described as a short intradiencephalic system (Björklund *et al.*, 1975; Lindvall *et al.*,

1974 b). The projections arise from perikarya located in the zona incerta (group A 13), and in the hypothalamic dopamine cell groups (A 11, A 14), to distribute widely in the hypothalamus, particularly in the dorsomedial and periventricular nuclei. In addition, some fiber tracts bend dorsally to reach the lateral septal nucleus (see: Moore and Bloom, 1978).

The periventricular dopamine system was first described by Lindvall and coworkers (Lindvall and Björklund, 1974; Lindvall *et al.*, 1974 b), as a complex fiber network coursing along the ventricles and aqueduct, from diencephalon to medulla. Neurons of origin are located in the A 11 and A 13 cell groups, from where they project rostrally and caudally along the dorsal longitudinal fasciculus of Schütz. Rostral projections reach the thalamus to innervate the medial and midline nuclei, and distribute also to several hypothalamic nuclei (Lindvall *et al.*, 1974 b). Descending axons probably end up in different brain stem nuclei, and, in addition, constitute the afore-mentioned diencephalo-spinal pathway.

Retinal Dopaminergic Cells

The first description of retinal catecholamine-containing cells was obtained in the rat by means of Falck-Hillarp's histofluorescence technique (Malmfors, 1963). Later studies have confirmed their presence in almost all animal species including man (Frederick *et al.*, 1982), and have supported their dopaminergic nature (see Brecha, 1983, for review). Morphologic observations have shown that dopaminergic retinal cells are regularly scattered in the inner part of the inner nuclear layer, where they reside among amacrine cells. In addition, sparse dopamine-containing somata can also be seen in the ganglion cell layer: they were originally denominated alloganglionic cells (Ehinger, 1966), but may well represent displaced inter-amacrine cells (Ehinger, 1976).

Although it has not been conclusively agreed on whether one or more dopaminergic cell types are present in the retina, it is currently believed that—at least in mammals—most retinal dopamine-containing perikarya belong to the interplexiform cell type (Brecha, 1983; Frederick *et al.*, 1982). This hypothesis is mainly supported by the distribution of dopamine-containing terminals, which are concentrated both in the outer and in the inner plexiform layers. Dopamine-containing processes located in the inner plexiform layer constitute a

dense stratification in lamina 1, and distribute sparsely to laminae 3 and 5; dopamine terminals are also seen in the outer plexiform layer, where they form a dense plexus, and in the inner nuclear layer, where they surround the GABAergic horizontal cells (Brecha, 1983).

Anatomo-functional Considerations

When considering their complex anatomical organization, it is expected that central nervous system dopaminergic pathways are involved in different functional roles. In fact, data obtained from the study of pharmacologically induced, or of naturally occurring alterations of central dopaminergic transmission support this view. Briefly it can be affirmed that dopaminergic neurons of the midbrain efferent system are presumably involved in extrapyramidal motor control, by means of the mesencephalo-striatal pathway (see Hornykiewicz, 1981, for review), and in behavioural and cognitive processes, by means of the mesencephalo-limbic and mesencephalo-cortical pathways (see Mayeux, 1981, for review). As reported above, tubero-infundibular neurons have been shown to control prolactin secretion, while diencephalo-spinal dopaminergic neurons are believed to act upon the spinal cord preganglionic sympathetic neurons (see, also, Lindvall *et al.*, 1983). Finally, while no definite role has been attributed to the incerto-hypothalamic and periventricular systems, the involvement of retinal dopaminergic cells in visual processes appears to be obvious.

Idiopathic Parkinson's disease is a pathological condition associated with global impairment of central nervous system dopaminergic activity. It is likely that all the central nervous system dopaminergic pathways are affected by the disease, since clinical symptoms include: impairment of extrapyramidal motor control, of cognitive abilities, of neuroendocrine functions, of visual performances, and of autonomic balance (see: Bodis-Wollner and Yahr, 1978; Marsden and Fahn, 1981). In addition, the finding that abnormal heath responses are present both in Parkinson's disease and in neuroleptic-induced parkinsonism, particularly after administration of drugs acting on dopamine receptors (Figà Talamanca *et al.*, 1985), allows to propose that some dopaminergic pathways (possibly, the incerto-hypothalamic neurons) may be responsible for thermoregulation. Certainly, further studies are required in order to draw thorough anatomo-functional correlations.

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