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Ventral tegmental (A10) system: neurobiology. 1. Anatomy and connectivity

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GENERAL INTRODUCTION

This review of the neuroanatomy of the ventral tegmental area (VTA) and its projections (VTA system) is the first of a series based on the types of activity and interactions found in this projection system. Thus issues that relate to neurotransmission and modulation will be discussed later.

The purpose of these articles is to provide a relatively succinct and informative summary of the present consensus of understanding of the VTA system paying due consideration to the historical development of the extensive interest that this system has received, particularly in the past 25 years. A qualified understanding of the anatomy and connectivity of the VTA provides the basis for discussion of the amazingly diverse involvement of the VTA system in the integration of information and the modulation of the organization of behavior in the central nervous system.

1. THE DISTRIBUTION AND NATURE OF NEURONS IN THE VTA

1.1. *Introduction*

The VTA consists of a few heterogeneous groups of cells lying together close to the midline on the floor of the midbrain (mesencephalon).

A short description of the major nuclei on which the VTA borders, shows the position of the VTA more precisely. Rostrally extend the mammillary bodies and the posterior hypothalamus (diencephalon). The nucleus (N.) ruber and oculomotor fibers are situated dorsolateral to the VTA. Dorsally and to some extent through the VTA pass fibers from several brainstem nuclei. These come to form the medial forebrain bundle (MFB) as it ascends from the midto the forebrain (telencephalon). In particular the raphe nuclei extend dorsally from the caudal border. Caudally to the VTA lies the pons and hindbrain (rhombencephalon).

The VTA lies bilaterally in the midline appearing very roughly semicircular in transverse section. In its caudal extent it lies over the N. interpeduncularis. Lateral to the VTA is the substantia nigra (SN) (Fig. 1).

1.2. *A historical point of view*

The VTA seldom received discussion as a separate entity before the development of current techniques using the axonal transport of labeled substances for the study of connections between brain areas. The classical description was made by Tsai[410,411] in 1925 from Golgi and Nissl preparations. In this description of the brain of the opossum he described an area lateral to the N. interpeduncularis, the 'trigonum interpedunculare', which consisted of the peduncularis corporis mamillaris, the lemniscus medialis and the N. tegmenti ventralis. This area lay medial to the 'trigonum lemnisci', that extended from the pes pedun-

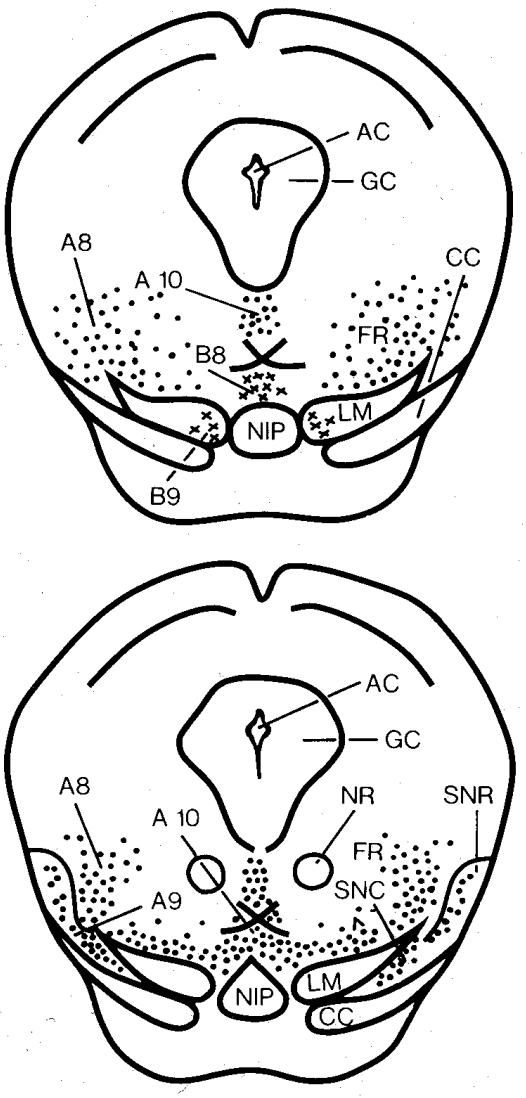

Fig. 1. Transverse sections through the rat mesencephalon at more rostral (upper diagram) and a more caudal level of the N. interpeduncularis (after Dahlstrom and Fuxe[87]). The topography of the DA cell groups A8–A10 and 5-HT cell groups B8–B9 are illustrated. AC, aqueductus cerebri; CC, crus cerebri; FR, formatio reticularis; GC, grisea centralis; LM, lemniscus medialis; NIP, N. interpeduncularis; NR, N. ruber; SNC/SNR, substantia nigra zona compacta/reticulata.

culi to the ventral tip of the SN where the sulcus lateralis mesencephali marked the separation from the tegmentum proper. The border of the trigonum interpedunculare coincides with the separation, on the grounds of histofluorescence and connectivity studies, between the dopaminergic (DA) cells of the A9 (SN) and the A10 (VTA) nuclei[87] (Figs. 1 and 2).

Kosaka and Hiraiwa[215] and Castaldi[72] believed that the fusiform nature of the cells of the N. opticus tegmenti and N. tegmenti ventralis warranted their inclusion as part of the SN. The same desire for synthesis was reflected by Hassler[165] who referred to the VTA as the N. niger suboculomotorius. Tsai, however, disagreed. He argued that the cell-free space overlying the sulcus, the smaller size of the cells and their close relationship to the tracti mammillo- and olfacto-tegmentalis pointed to the specific character and function of the area — the area that has become known as the ventral tegmental area of Tsai.

The goal of a definition of the borders to a given brain region is to assist in the attribution of function to the connecting neural systems and to be able to make a contrast with related systems nearby. Neurobiologists have had a great deal of difficulty in defining the borders of the VTA.

Recent refinements in the study of the connections made by neurons in the VTA have demonstrated that a gradual change occurs across the sulcal area. This has been done with particular reference to the DA containing neurons of the ventral tegmentum. A continuum stretching from the A8 cells dorsolateral to the SN pars compacta to the A10 cells in the midline has been advocated[111,362,364,418]. This is argued on the basis that there is a gradient rather than a clear-cut difference between the structures innervated by these neurons.

Nonetheless there are some reasons for maintaining that there is a border worthy of recognition both on the basis of the principle target areas for projection, the pattern of innervation and the cytoarchitecture. These reasons will become evident from recent work showing differences in the structure and connectivity of the nuclei making up the VTA. (At this stage it should be emphasized that although much of the following discussion refers to the special feature of DA containing cells, it should be remembered that there are many neurons present that use other transmitters.)

1.3. *The A10 nuclei*

The cells in the area of contention on the lateral borders of the A10 area are known as the *N. paranigralis* (Npn). Dahlstrom and Fuxe[87], like the authors

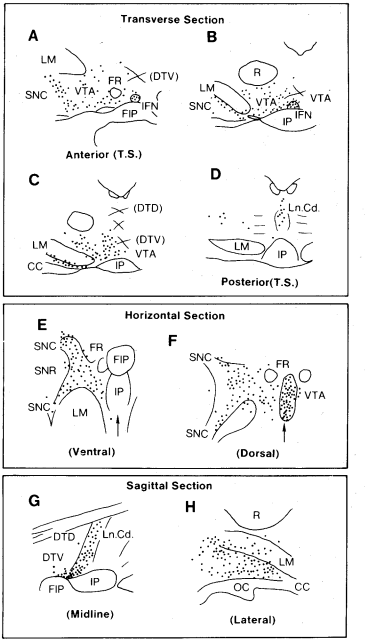

Fig. 2. Frontal sections (A–D) showing outlines of structures in the ventral tegmental region with dots representing the position and approximate density of DA cell bodies (glyoxylic acid-treated material) from anterior (A) to posterior (D) in the rat. Horizontal sections (E, F) were taken at a dorsal and ventral level through the N. interpeduncularis (E) and interfascicularis (F). (Arrows indicate the midline.) Sagittal sections (G, H) were taken at the level of the III nerve rootlets and in the midline (anterior is left). CC, crus cerebri; DTD/DTV, dorsal/ventral tegmental decussations; FIP, fossa interpeduncularis; FR, fasciculus retroflexus; IFN, N. interfascicularis; IP, N. interpeduncularis; LM, lemniscus medialis; LnCd., N. linearis caudalis; OC, oculomotor III; R, N. ruber; SNC/SNR, substantia nigra pars compacta/reticulata; VTA, ventral tegmental area (Phillipson[315]).

of most succeeding studies of rats, emphasized that there was no clear border between the A9 (SN) and the A10 (VTA) fluorescing cell bodies (i.e. containing DA). Nonetheless in their opinion, the A9 catecholamine cell bodies are those found around the border of the non-fluorescing N. tractus opticus basalis.

A number of authors maintain that a separation of the Npn from other cell groups can be seen in the brains of carnivores and primates. A clear separation from other nuclei of the VTA and SN has been well shown in the human[284]. More recently an immunocytochemical study of tyrosine hydroxylase (an enzyme important for DA synthesis) in the human brainstem found two distinct, closely packed groups of positively reacting cells at and below the exits of the third nerve. These nuclei correspond to the Npn and the N. parabrachialis pigmentosus (Npbp)[313].

A common origin for the Npn with the other cell groups of the SN and VTA may be indicated by the two types of cell present. The smaller cells resemble those of the Npbp (A10), whereas the larger cells resemble those of the SN (A9)[360,408].

From Golgi preparations Phillipson[316] noted a further distinction. Whereas the dendrites in the SN are organized in horizontal and vertical planes, he saw no long vertical dendrites in the VTA. However, Felten and Sladek[124] found that in 3 species of primate small cells of the dorsal, but not the ventral, A10 region gave rise to long vertical dendrites.

The rostral end of the VTA borders on the diencephalon. This coincides dorsally with the anterior limit of the N. ruber. Here the cells of both the dorsal and ventral interstitial nuclei[330] contribute along with cells in the rest of the VTA to the MFB. The ventral nucleus has been attributed to the diencephalon[203]. In the midline, caudal to this nucleus, over the fossa interpeduncularis, lies the *N. interfascicularis* (Nif)[45,315].

The Nif contains small, tightly packed cells which show a low fluorescence intensity with the glyoxylic acid method[315,408]. The latter authors[408] found that

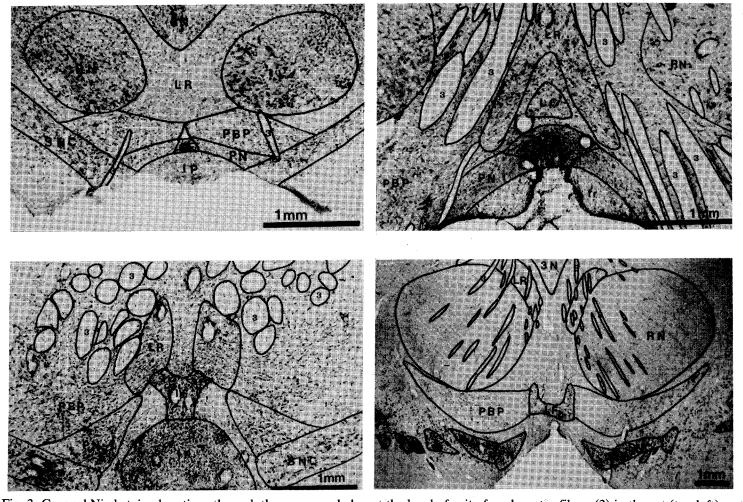

Fig. 3. Coronal Nissl-stained sections through the mesencephalon at the level of exit of oculomotor fibers (3) in the rat (top left), cat (top right), monkey (*Macaca nemestrina*) (bottom left) and man (male 65 years old) (bottom right) (Halliday and Tork[158,160,161]).

spindle shaped cells with a long dendrite throughout the VTA were absent in the Nif of cats. Monkeys are reported to have fewer but larger Nif neurons than rats or cats[324].

Although the Nif is the most rostral of the VTA nuclei, DA containing cells of the Npn also extend rostrally, dorsolateral to the Nif. Dahlstrom and Fuxe[87] noted that these cells extended into the N. interstitialis ventralis tegmenti between the fascicula retroflexi. Scattered fluorescent cells of the diencephalic A11 group extend caudally, medial and ventral to the fascicula retroflexi, towards the A10 cells. (cf. Figs. 2 and 3).

Thus, as with the definition of the lateral borders of the VTA, it may be seen that (1) the cytoarchitectonic borders do not closely coincide with the rostral extent of the DA containing cells; (2) the extension of the distribution of DA containing cells beyond the conventionally described nuclei of the ventral tegmentum results in a diffuse border area at the rostral limits of the VTA (i.e. borders with A8 and A11 nuclei).

The Npbp forms a mantle of relatively small, round, oval or stellate cells dorsal and dorsolateral to the N. interpeduncularis and ventral to the lemniscus medialis (Nissl preparations[315,360,408,410,411]). Larger cells in the cat show larger dendritic fields[160,161,408]. The cells seem to lack any consistent orientation. This contrasts with the rostrodorsal/caudoventral orientation in the Npn and the caudodorsal/rostroventral orientation in the N. linearis caudalis[315]. In terms of fluorescing DA cells the Npbp is limited in the rostrocaudal axis to the middle two thirds of the N. interpeduncularis.

A10 cells distribute dorsally in the *N. linearis* (Nln). The tegmental decussation forms the lateral boundary. Some DA cells are even found dorsally amongst the raphe group[263]. The pars caudalis extends from the rostral end of the N. interpeduncularis back over the caudal midline[315]. The pars centralis and rostralis extend rostrally from the Npbp[45,386]. Taber[395] distinguished an intermediate part in the cat. It is very small[325,431] and may correspond to the caudal part of Huber et al.[186]. The cells of the Nln are mainly medium sized and oval or fusiform in shape. But smaller rounder cells have been observed in the rat[360]. To Tork et al.[408] there was a larger size range apparent in the rostral linearis-parabrachial continuum of the cat compared to the interfascicular and caudal parts. Indeed Poitras and Parent[325] thought the cells in the pars rostralis to be larger. These larger, more pyramidal cells have large dendritic fields (Fig. 4). The smaller oval cells are characterized by relatively few spines. As with the Nif the border between the Nln rostralis and the A8 is arbitrary[211].

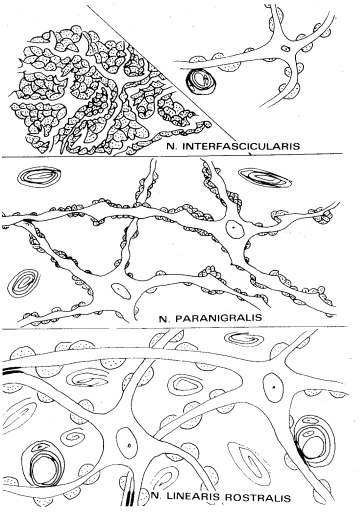

Fig. 4. The main ultrastructural features of 3 VTA nuclei drawn from electron micrographs. These representations show internal sequestration of the Nif (rostral is left), varicose dendrites in the Npn and smooth cylindrical dendrites in the Nln rostralis (Tork et al.[408]).

In summary it is widely agreed that the VTA A10 group of cells consists of essentially separate nuclei — the Npn, Npbp, Nln caudalis and rostralis, and Nif[87,301,315] (Table I).

1.4. *Phylogenetic representation of DA systems*

Already it is clear that the presence of dopamine (DA) containing cells in the VTA has obtained an overwhelming significance for neurobiologists concerned in defining the VTA. DA was first recorded in

the CNS at the end of the fifties[268,429] and soon localized intraneuronally[68]. These demonstrations were rapidly followed by the formal classification of the DA cells of the VTA as the A10 group[87].

Soon DA cells were located in fish[221], birds[128] and in a range of mammals[129] (Table III). In lower vertebrates the 'peripeduncular area' contains a mixture of both DA and serotonin (5-HT) cells[105]. The latter are more abundant in primitive fish and amphibia. Although catecholamine cells are present by the oculomotor roots and CA processes have been seen in the pallium, a broader development is seen in only a few teleosts and reptiles.

Since 1964 all studies have emphasized an astonishing general similarity between the VTA nuclei of mammals ranging from rodents to man: e.g. rat[229, 315–317], rabbit[56], dog[360], cat[45,320,325,395], opossum[85], non-human primates[125,138,185,191,398] and man[60,284, 293–296,313].

In detail there are slight differences (e.g. rostrolateral extent of the VTA cf. Nln in 1.3. above). Subgroups of the VTA may show changes in the dorsal extent. The dorsal peak of A10 cells may be more extensive in primates. In particular this was seen in the squirrel monkey rather than in two old world species of macaque. The cells even stretch dorsomedial to the N. ruber[124,398].

1.5. *Comparative representation of DA*

A Swedish group has estimated that the average DA neuron contains 30 pg DA[369]. It has been estimated that there are 27–29,000 cells (bilaterally) in the VTA of the rat[159,161,386]. Of the 18,000 staining for tyrosine hydroxylase (TOH)[386] most were concentrated in the middle third of the area from the Nif and Nln. For the rat this is the greatest midbrain concentration of DA (i.e. A10 > A9; 2.3/2.4:1 for rat and cat, 1:1.5/1.6 for primates[61,141,159,161]).

The number of DA cells increases with phylogenetic progression. Using a similar method to Swanson[386], German et al.[141] estimated the number of cells in the A9/A10 area as 25,000 for the Balb/C mouse, 40,000 for the albino rat and 450,000 for a 33 year-old man. (Close comparisons between studies cannot be

TABLE I

Volume (V) of each nucleus in mm³ and the total number of cells (n) in the SNC and each nucleus of the VTA for rat, cat, monkey and man

Percentages are expressed in brackets below each value, in respect of the total volume and cell population of the VTA. SNC, substantia nigra pars compacta; VTA, ventral tegmental area; PBP, N. parabrachialis; PN, N. paranigralis; IF, N. interfasicularis; LR/LC, N. linearis rostralis/caudalis (Halliday and Tork[161]).

Species	*SNC*	*VTA*	*PBP*	*PN*	*IF*	*LR*	*LC*
Rat							
V	0.3	1.2	0.6	0.3	0.1	0.1	0.2
(%)		(100)	(50)	(23)	(9)	(5)	(13)
$n \times 10^3$	12	27	11	7	6	0.8	2
(%)		(100)	(40)	(26)	(23)	(3)	(8)
Cat							
V	3	14	6	2	1	3	3
(%)		(100)	(42)	(13)	(7)	(19)	(19)
$n \times 10^3$	26	63	18	7	12	10	16
(%)		(100)	(29)	(12)	(19)	(16)	(25)
Monkey							
V	6.3	6.5	4.5	0.7	0.2	0.3	0.8
(%)		(100)	(69)	(11)	(4)	(4)	(13)
$n \times 10^3$	71	47	37	6	2	0.5	2
(%)		(100)	(77)	(13)	(4)	(1)	(5)
Human							
V	68	183	101	33	4	9	37
(%)		(100)	(55)	(18)	(2)	(5)	(20)
$n \times 10^3$	436	690	288	256	46	17	83
(%)		(100)	(42)	(37)	(7)	(2)	(12)

made because of the use of different correction factors (Bogerts and Swanson) and observational vs automatic counting methods (Halliday and German) where programmed criteria may have allowed small cells to be omitted.) The cut-off point for A10/A9 differences in phylogeny may occur with *Tupaia* (but cf. dog[360]). *Tupaia* is arguably at the base of the primate lineage. In this animal a histofluorescent study found the A10 area to be less extensive than in the rat[272]. It seems to be agreed, according to present criteria, that in man there may be more DA neurons in the SN than in the VTA[61,141,174]. This is reflected by the DA levels in the VTA (ca. 2.4 ng/mg protein) which are half those of the SN pars compacta[321].

We shall see in the following sections that the only remarkable phylogenetic change is that of the DA projections accompanying the explosive growth of the neocortex in mammalian evolution[36,252] (see 2.2.7. below). In non-mammals it is not surprising that a mesocortical projection has not been clearly shown. More surprising is the purported absence of a mesostriatal DA pathway in fish[308].

1.6. *Types of activity*

Two types of cell may be made out with the light microscope in the A9 and A10 after treatment with Toluidine blue and Nissl stain[102,379]. A lightly staining type is probably of a non-DA nature. But darkly stained basophilic cells probably represent somata of DA neurons. The latter type was shown to take up tritiated catecholamines which disappeared after treatment with the specific catecholamine toxin 6-hydroxydopamine (6-OHDA).

These authors also obtained electron microscopic results essentially similar to those of the SN[173,355,378]. The basophilic (DA) cells contained densely filled ribosomes and large quantities of rough endoplasmic reticulum. In the lightly staining cells ribosomes were

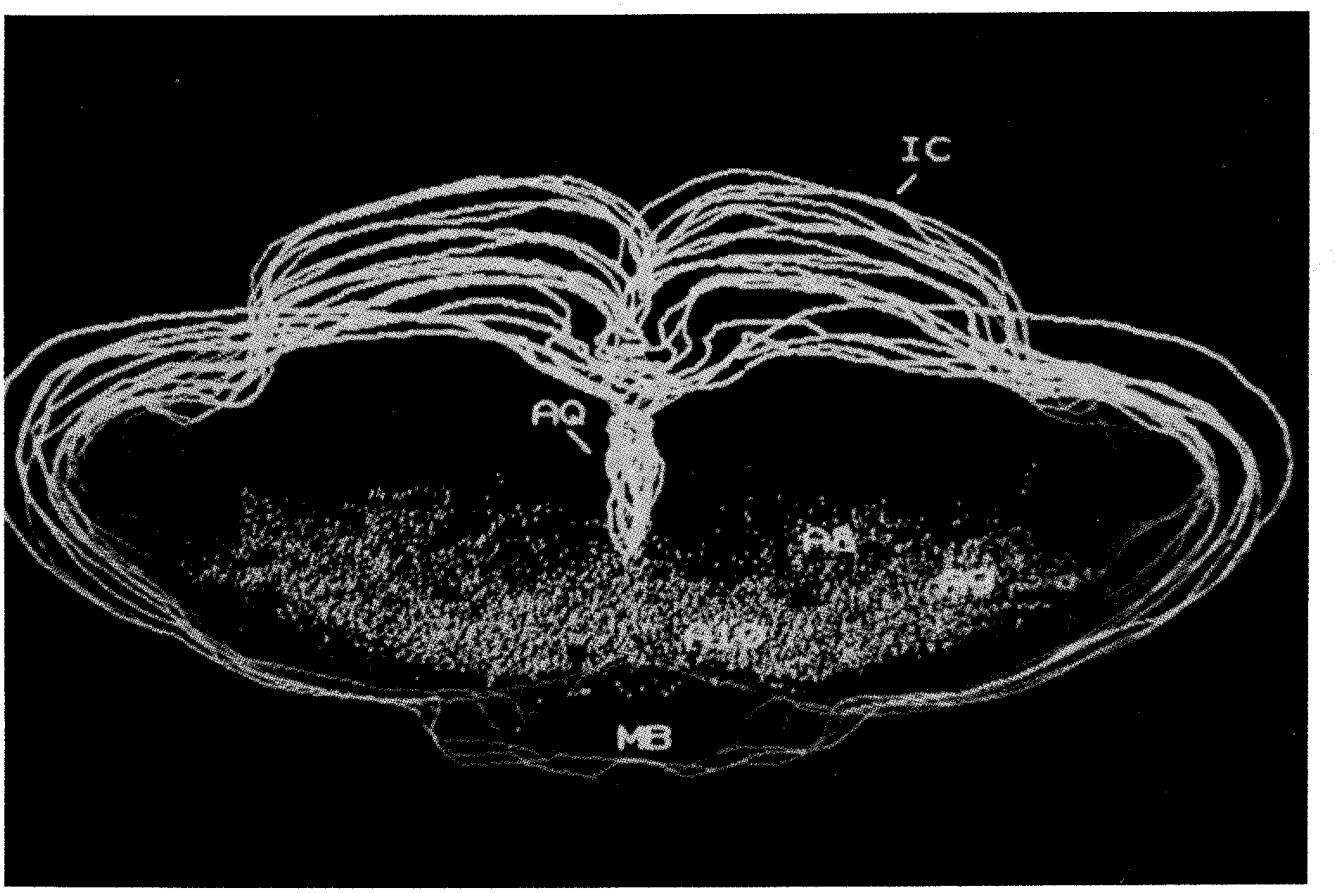

Fig. 5. Three-dimensional computer reconstruction of midbrain (rostral in foreground) DA cell distribution identified by TOH immunohistochemistry in the rat. Labelled are the DA cell groups A8–A10. AQ, cerebral aqueduct; IC, inferior colliculus; MB, mammillary bodies (German et al.[141]).

sparse and the reticulum well spaced; in contrast to the DA cells, the nuclear membranes showed many involutions.

Types of DA cell in the VTA have been separated according to their rate of monoamine metabolism by following the decline of histofluorescence after blockade of DA synthesis[2]. The turnover rate for DA was reported to be slightly higher in the smaller more medial cells of the Nif and Nln than in the more lateral Npn. The more peripheral cell bodies are more likely to be non-monoaminergic as fewer fluoresce.

Melanin pigment is found in the A10 (and other monoamine nuclei) of man, although the Nif has not been specifically described[60]. There may be many more (60 times) pigmented neurons in the A9 than the A10 (ref. 61). The pigment accumulates from the first through the 6th decade[148]. To a lesser degree pigment granules are found in other primates[124]. It has been hypothesized that this substance is less a metabolic waste product as a physiological modulator of receptor function (discussion[199]). Indeed it has been suggested that melanin granules may promote the dynamics of the agent (cf. MPTP[243]) that affects the availability of DA in Parkinson's disease.

Another feature of the VTA that affects activity is its vascularization. Apposition of the basement membrane of blood capillaries to the plasma membrane of somata and dendrites has been observed in new and old world primates[123,124]. In contrast to the observations of these authors on rats and rabbits, an Australian group has consistently found that a large number of cells (and dendrites) in the midline nuclei of

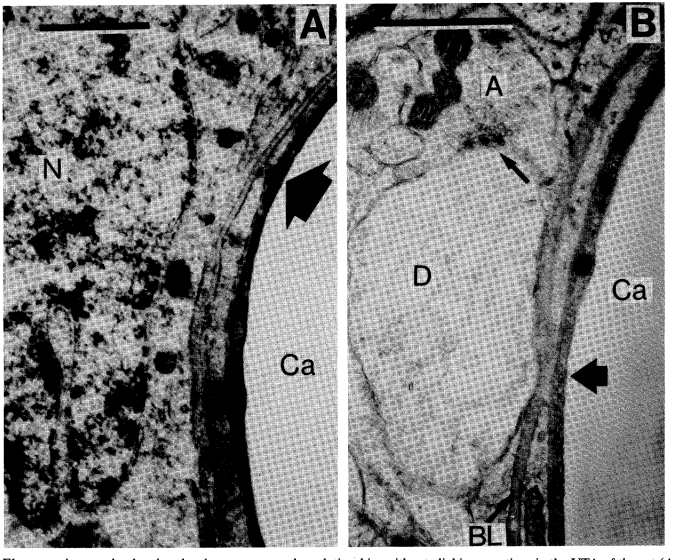

Fig. 6. Electron micrographs showing the close neurovascular relationship, without glial intervention, in the VTA of the rat (A) and cat (B) (Bar = 1 μm). In the rat VTA the perikaryon is in close contact with the blood–brain barrier (small arrow points to a synapse; N, nucleus). In the cat VTA a dendrite (D) is in close contact with the capillary (Ca) (BL, basal lamina; A, axon)). Large arrows point to pores in the basement membrane. (Halliday and Tork[158,160,161]).

cats[158,408] and in all the VTA nuclei of the rat[160] abut on to the walls of blood vessels (Fig. 6). This feature is also characteristic of other monoamine nuclei.

1.7. *A caveat on experimental lesion damage*

The majority of neuroanatomical, neurophysiological and behavioral studies of the VTA involve the implanting of cannulae or electrodes. The intention may be to cause damage chemically or electrolytically. But unintentional damage from the electrode or cannula tracts may also occur. It is therefore appropriate to consider briefly the difficulties that arise for the interpretation of lesion effects.

Mechanical (electrolytic) and chemical lesions are used in anatomical and behavioral studies. In the former degenerating fibers are picked up by silver impregnation or the Falck–Hillarp formaldehyde fluorescence technique (for example). In the latter electrolysis and specific catecholamine toxins (e.g. 6-OHDA) are used to investigate the behavioral changes resulting from the denervation of the VTA projection areas. These, as well as other methods for anatomical labelling (e.g. glyoxylic acid, horseradish peroxidase (HRP), tritiated amino acids) and psychopharmacological techniques (injection of DA agonists and antagonists) can produce non-specific damage to fibers of passage. These fibers can be noradrenergic (NA)[9], serotonergic[412] and peptidergic[175]. These fibers pass both around and through the VTA. Specifically there is the ventral NA bundle that joins the MFB to project to the hypothalamic complex, basal ganglia, lateral septum and medial amygdala. Damage to the peduncularis mammillaris can also affect innervation of the lateral hypothalamus, preoptic and medial septal areas. Anterior thalamic innervation is interrupted when the lemniscus medialis and peduncularis cerebellaris superior are invaded by large lesions. Damage to the fasciculus retroflexus would interrupt further diencephalic connections. It is not difficult to damage the connections of the N. interpeduncularis with ventral midline VTA lesions.

Having suggested that caution be taken with the interpretation of the results of lesions in the VTA, we should add that in some cases care has indeed been taken to ensure that non-specific damage, such as that caused by the toxin 6-OHDA, be kept to a minimal level[134,366]. Yet well-intended attempts to restrict the extent of lesion damage to a small area lead to a second problem. Small lesions will not affect the whole VTA. Thus on the one hand, where 6-OHDA is used to damage A10 cells in the dorsal part of the VTA, it is likely to damage cells of the A8 area lying medially in the tegmentum (cf. Figs. 1 and 5 in Dube and Parent[104]). On the other hand electrolytic damage of the posterior VTA is likely to affect the rostrally lying 5-HT cells of the B8 group that lies in part under the Nln caudalis. Many studies that have tried to avoid these problems with small lesions have not investigated the full extent of the VTA A10 region. The advantages and disadvantages should be borne in mind during the following discussion.

2. THE CONNECTIVITY OF THE VTA

2.1. *Intrinsic connections*

Within the VTA of primates[124] and subprimates (cat[158,161]) there is a high proportion of dendrodendritic contact. Both laboratories report that about 50% of cells have dendrosomatic, axodendritic, dendrodendritic but not axosomatic synapses. Long fluorescing dendrites (100 μm+) have been seen in both the A10 and the A9 region[124]. Indeed the dendritic fields of the Npbp can invade the Npn area and those of the caudal Npn region enter the interpeduncular zone. This further emphasizes the high degree of DA/non-DA and local integration that must occur throughout the A10 nuclei[316]. The absence of local axosomatic synapses is also a feature of other monoaminergic nuclei.

Phillipson[316] reported local axon circuits from type 1 cells with varicose secondary dendrites that make up the Nif, Nln and to a lesser degree the Npbp of rats. (The Npn and Npbp have primary and secondary dendrites that are moderately spiny.) However, in view of the difficulty of excluding some artifacts in Golgi material it is probable that this second form of intra-VTA communication is but sparsely represented.

2.2. *Efferent connections*

We will first consider the range of structures to which the VTA projects, more or less, as a whole. Reports on the localization of the cells of origin within the VTA will be considered in the next section. The emphasis is placed on establishing the total range of projections irrespective of the transmitter in-

volved. An attempt to indicate where there are DA and non-DA pathways may be found in Fig. 7. As a generalization, it has been suggested that about 30% of VTA projections do not contain DA[403]. For comparison, estimates for the SN range from 5 to 20%[414].

2.2.1. *The terminology for VTA pathways.* Five VTA systems of efferent fibers are distinguished (Table II). The term 'mesostriatal' pathway refers to the VTA projection upon the anteromedial and ventral neostriatum. For SN and VTA projections there is a decreasing concentration gradient of DA away from these areas. The SN provides 80% of the DA found in the neostriatum[103]. In the anteromedial ventral direction there is an increasing participation of the VTA projection (see below).

The N. accumbens septi (to be referred to as the accumbens) (Ziehen cited ref. 202), despite being called the ventral striatum[167] or fundus striati[413] is still widely accepted as a 'limbic' structure because of its connectivity and despite the embryological, cyto- and myeloarchitectonic reasons for considering it as part of the neostriatum[63]. Further, recently fine morphological differences between DA terminals in the accumbens and dorsal neostriatum have been described[62]. The accumbens is therefore considered part of the mesolimbic and not of the mesostriatal system. This does not imply any necessary fundamental differences from the remaining 'striatum' in terms of its origin or organization.

The term 'mesolimbic system' was first brought into use by Ungerstedt[412]. However, neither the term 'mesolimbic' nor 'limbic system' has received an un-

TABLE II

Central dopaminergic projection systems

For further details of VTA connections, see text; for SN connections, see discussions and citations in Usunoff et al.[413], Bentivoglio et al.[35], Dray[103]; for non-SN/VTA DA systems see Lindvall and Bjorklund[230], Lindvall et al.[234], Miachon et al.[263], Kalia et al.[200].

System	*Origin*	*Major innervation*
Not involving VTA		
Retinal	Inner nuclear layer	Dendritic projections
Periglomerular	Olfactory bulb	Dendritic projections
Tuberoinfundibular	A12: periventricular and arcuate hypothalamic nuclei	Pituitary (median eminence)
Incertohypothalamic	Zona incerta, A11, A13: dorsal caudal and A14: periventricular hypothalamus	Zona incerta, preoptic Periventricular hypothalamus
Periventricular	Mesen- and thalamocephalic, Periaqueductal gray	Periaqueductal gray, Medial thalamus and hypothalamus
Rare neurons	Area postrema, B nuclei, dorsal motor n. vagus, decussatio brachium conjunctivum, fasciculus longitudinalis medialis	Refs. 200, 263
Involving VTA A10 (and A8, A9)		
Mesostriatal	SN (VTA)	Anteromedial striatum
Mesocortical	VTA (SN)	Prefrontal (pregenual) and insular (suprarhinal) cortices
Mesolimbic	VTA (SN)	Limbic cortices, septo-hippocampal complex, accumbens, amygdala
Mesodiencephalic	SN (VTA) (VTA) SN	Several thalamic nuclei, Several hypothalamic nuclei
Mesorhombencephalic	SN and VTA SN (VTA)	Monoaminergic nuclei, Superior colliculus, reticular formation and periaqueductal gray, Spinal cord
	SN	

ambiguous and widely accepted definition. Here the term '...limbic' will cover the accumbens, the paleo- and archicortices (including amygdala), the supragenual, cingulate cortex[244,303] and the transitional entorhinal cortex, that for functional reasons can be subsumed as part of the hippocampal complex[386].

The term 'mesocortical system' refers to the projections to the neocortices as well as those cortices showing a slight transitional character (peri/suprarhinal, insular, orbital). For the 10 years since their discovery the mesocortical projections have largely been claimed to be restricted to the pregenual frontal and transitional cortices. Now it is becoming clear that there are also projections to sensory, motor and association areas (e.g. temporal cortex) in rodents, carnivores and primates[41].

This scheme differs slightly from that of some previous authors[230], but draws a better compromise between anatomical characteristics and brain regions that appear to function together as a subsystem. The conventional terminology omits reference to projections to the mid- and hindbrain (mesorhombencephalic) and those to the 'tween brain (mesodiencephalic).

2.2.2. *The mesorhombencephalic pathway.* There are projections to the major monoaminergic cell groups. Fibers to the SN project more upon the pars compacta than the reticulata. The A9 rather than the A8 cell group appears to be in receipt of this ipsilateral projection[32].

The report of Beckstead et al.[32] further described the presence of label in the midline tegmentum (level of the rostral pole of the inferior colliculus), rostral margin of the median and dorsal raphe (cf. ref. 127), alongside the trochlear nucleus and in the dorsal and ventral parabrachial areas. The caudal limit for the spread of label occurred adjacent to the N. tegmenti dorsalis lateralis and locus coeruleus (LC).

It has been suggested from the high level of DA to be found in the dorsal raphe and LC that a few DA containing cell bodies may be present[423]. This has been confirmed for the raphe but not for the LC[263]. But there are DA containing terminals in the raphe and LC[230,290]. Simon et al.[362-364,367] have confirmed bilateral projections to these nuclei and to the central gray. But in contrast to the report of Beckstead they found label in both dorsal and ventral tegmental nuclei of Gudden.

Swanson[386] found that the majority of these fibers were non-DA, but more DA containing fibers (upto 33%) were found to originate more rostrally (Nif). Levels of DA in the LC were reported to fall by 46% after VTA damage[258]. The VTA sends twice as many fibers to the LC as the SN pars compacta. (Caveat: there is a large projection from the LC to the N. interpeduncularis[386].)

As first pointed out by Simon[362] there are at least two more non-DA descending pathways[119,406]. The lateral path (rubrospinalis) projects to the nucleus of the facial nerve, the superior olive and particularly to the inferior olive in the rat[143a,392], rabbit[143a,249] and opossum[255,256].

A more medial path descends to the pontine tegmental and raphe nuclei and the bulbar reticular formation. (But the possibility that the lesion invaded the efferent pathway from the N. Darkschewitsch[391] should be noted.) Further degeneration into the spinal cord has not been reported (contrast SN lesions). There is no clear demonstration of DA fibers descending from the VTA A10 (Fig. 7).

Of great interest from a functional point of view are projections to the vestibular and accessory oculomotor nuclei (N. cuneiformis, reticularis pons oralis, interstitialis of Cajal and Darkschwitsch). The retrograde tracing study of Giolli et al.[143a] shows that these projections arise from the Npn and particularly the dorsolateral Npbp.

The autoradiographic study of Simon et al.[364] reported a cerebellar projection of the VTA. Although a pharmacological study[257] also reports the presence of possible DA uptake sites here, other anatomical work using injections of true blue[386] did not replicate these findings.

2.2.3. *The mesodiencephalic pathway.* Details and citations of reports on diencephalic and telencephalic VTA efferent projections are summarized in Tables III and IV. After injection to the VTA label has been reported from the posterior and medial hypothalamus, from the supraoptic nucleus and the median eminence. The connection with the medial hypothalamus has received indirect confirmation from neurophysiological study[25,26]. A few hypothalamic cells could be driven by VTA stimulation. The possibility of direct projections to the lateral hypothalamus and lateral preoptic area has also been confirmed. But it should be mentioned that others have looked for pro-

TABLE III

Historical sequence, techniques and animals used in the selected anatomical studies cited on the VTA projection system of birds and mammals, with special reference to DA-ergic projections (1957–1984)

AA^+, radioactive amino acid label (e.g. Leu, Pro), anterograde transport; D, degeneration following lesion, usually with Fink-Heimer or Nauta-Gygax, silver staining method; DA^+, radioactive dopamine — study of transport/synthesis; HF, histofluorescence studies (originally Falck-Hillarp method with formaldehyde, later glyoxylic acid for condensation) or immunohistochemical (IR) techniques (DBH, dopamine β-hydroxylase); new modifications (e.g. color — (Col), Evans blue, Nuclear yellow etc.); HRP, horseradish peroxidase (both antero- and retrograde transport studies); Ph, pharmacological analysis of monoamines, with/without lesion; WGA, wheat germ agglutin transport; M/F, male/female (where not stated, the information was not presented in the original report).

Study	*Technique*	*Animals*
1957		
Guillery[152]	D	rat
Montagu[268]	HF	chick, rat, rabbit, guinea pig and man
Weil-Malherbe and Bone[429]	Ph	rabbit
1958		
Nauta[275]	D	cat
1959		
Guillery[153]	D	cat
1963		
Bogdanski et al.[59]	Ph	rat, rabbit, pigeon, chicken
1964		
De Vito and Smith[94]	D	monkey (*M. nemestrina*)
Dahlstrom and Fuxe[87]	HF	M rat
1965		
Fuxe[127]	HF	M rat
Fuxe and Owman[129]	HF	rat, guinea pig, rabbit, cat, dog and monkey
Fuxe and Ljunggren[128]	HF	pigeon
Molina[267]	D	cat
1966		
Wolf and Sutin[433]	D	M rat
Anden et al.[9]	HF	M rat
1967		
Juorio and Vogt[198]	Ph	chicken
1968		
Akagi and Powell[3]	D	cat
Pin et al.[320]	HF	cat
1969		
Llamas and Reinoso-Suarez[236]	D	cat
1971		
Ikeda and Gotoh[188]	HF	chicken
Ungerstedt[412]	HF	rat
1972		
Batista et al.[28]	HF	monkey
1973		
Nobin and Bjorklund[284]	HF	human (foetus)
Thierry et al.[404,405]	Ph^+	M rat
Olson et al.[293–295]	HF	human
Bjorklund and Nobin[52]	HF	M and F rat
1974		
Lindvall and Bjorklund[229]	HF	M rat
Kopin et al.[214]	HF (Ph)	M rat
Jacobowitz and Palkovits[192]	HF (Ph)	M rat
Brownstein et al.[65]	Ph	M rat
Lindvall et al.[235]	HF	F rat

(Table III continued)

Study	*Technique*	*Animals*
Hökfelt et al.[176,177]	HF (Ph)	M rat
Berger et al.[40]	HF	M rat
Simon et al.[366]	D	rat
Hubbard and Di Carlo[185]	HF	monkey (*S. sciureus*)
Felten et al.[125]	HF	monkey (*M. mulatta*)
Lidbrink et al.[227]	Ph	M rat
Conrad et al.[82]	AA^+	M rat
Segal and Landis[357]	HRP	M rat
Fuxe et al.[131]	HF	rat
1975		
Fuxe et al.[130]	HF	M rat
Swanson and Hartman[390]	HF (DBH)	M rat
Garver and Sladek[138]	HF	monkey (*M. speciosa*)
Bobillier et al.[57]	AA^+	cat
Lindvall[228]	HF	F rat
Hopkins[181]	HRP	rat, cat and *Rhesus* monkey
Koob et al.[213]	Ph	M rat
Swanson and Cowan[387]	AA^+	M and F rat
Llamas et al.[237]	HRP	cat
1976		
Conrad and Pfaff[80,81]	AA^+	M and F rat
Fallon and Moore[114,115]	HF	M and F rat
Taber-Pierce et al.[396]	AA^+	cat
Shimada et al.[360]	HF	dog
Beckstead[30]	HRP	M and F rat
Simon et al.[367]	D	M rat
Swanson[385]	AA^+	M and F rat
Tassin et al.[399]	DA^+	M rat
Benowitz and Karten[34]	HRP	pigeon
Avendano et al.[16]	HRP	cat
Bockaert et al.[58]	Ph	M rat
Berger et al.[39]	HF	M rat
Kizer et al.[208]	Ph	M rat
1977		
Collier and Routtenberg[79]	HF	M rat,
Meibach and Siegel[261]	HFP/AA^+	M rat,
Simon and Le Moal[363]	D	M rat,
Assaf and Miller[15]	HRP	M rat
Pasquier et al.[311]	HRP	rat,
Brown and Goldman[64]	Ph	*Rhesus* monkey
Herkenham and Nauta[169]	HRP	M and F rat
Yamamoto et al.[439]	HF	bird (*Melopsittacus undulatus*)
1978		
Bjorklund et al.[54]	Ph	monkey (*C. aetiops*)
Divat et al.[98]	HF/HRP	rat, opossum (*D. viginiana*), tree shrew (*T. belangeri*)
Lindvall et al.[233]	HF/HRP	M and F rat
Lindvall and Stenevi[231]	HF/HRP	F rat
Ottersen and Ben-Ari[299]	HRP	rat
Moore[270]	HRP/AA^+	F rat
Blessing et al.[56]	HF	M rabbit
Poitras and Parent[325]	HF	M and F cat
Crutcher and Humberstone[85]	HF	opossum,
Emson and Koob[108]	DA	M rat,
Troiano and Siegel[409]	AA^+	M and F cat,
Jacobowitz and Maclean[191]	HF	pygmy marmoset (*Cebuella* sp.)
Krettek and Price[219]	AA^+	rat and cat
Ochi and Shimizu[290]	HF	M and F rat
Beckstead[31]	HRP	F rat

(Table III continued)

Study	*Technique*	*Animals*
Fallon et al.[117]	HF	F rat
Fallon and Moore[114, 115]	HF	F rat
Bentivoglio et al.[36]	HRP	cat
Schwab et al.[353]	WGA	M rat
Nauta et al.[279]	AA^+	rat
Phillipson[314]	HRP	F rat
1979		
Pearson et al.[312]	IR	human
Gilad and Reis[143]	DA^+/Ph	M and F rat
Arikuni and Gotoh[13]	HRP	rabbit
Herkenham and Nauta[170]	AA^+	M and F rat
Simon et al.[364,368]	HRP/AA^+	M rat
Phillipson[315–317]	HRP/HF	F rat
Bischoff et al.[48]	Ph	M rat
Beckstead et al.[32]	AA^+	M and F rat
Haglund et al.[157]	DA^+	M rat
Smialowski et al.[372]	Ph	rabbit
Wyss et al.[437]	HRP	rat
Lewis et al.[224]	HF	M rat
Russchen and Lohman[343]	HRP	cat
1980		
Veening et al.[418]	HRP	rat
Amaral and Cowan[8]	HRP	monkey (*M. fasicularis*)
Scatton et al.[351]	Ph	M rat
Szabo[343]	HRP	cat
Szabo[394]	HRP	monkeys (*M. irus and mulatta, S. sciureus*)
Luiten and Room[241]	HRP	M rat
Phillipson and Griffiths[318]	HRP	F rat
Cronister et al.[76]	HRP	rat and rabbit
Groenewegen et al.[150]	HRP	cat
Nitecka et al.[283]	HRP	M and F rat
Vincent et al.[424]	Ph	M rat
Newman and Winans[280,281]	HRP	M golden hamster
Mehler[259]	HRP	monkey
Shen and Anderson[358]	AA^+	guinea pig
1981		
Markowitsch and Irle[252]	HRP	M and F cat
Tork and Turner[407]	HRP/HF	cat
Somogyi et al.[375]	HRP	rat
Room et al.[340]	AA^+	cat
Palacios et al.[300]	Ph^+	rat
Fallon[111]	HF (Col)	M and F rat
Fallon[112]	HF/AA/HRP	F rat
Bogerts[60]	melanin count	human
Herrling[172]	Ph	M and F rat
Wang[427]	HRP/HF (col)	M rat
Barone et al.[26,27]	HRP	M rat
Krayniak et al.[216, 217]	HRP/AA^+	rat, monkey (*S. sciureus*)
Van der Kooy et al.[415]	HF	M rat
Dube and Parent[104]	HF	chicken
Ottersen[298]	HRP	rats and cats
1982		
Phillipson and Pycock[319]	Ph	F rat
Albanese and Bentivoglio[5]	HF (col)	rat
Velayos and Reinoso-Suarez[420]	HRP	cat
Porrino and Goldman-Rakic[326]	HRP	monkey (*M. mulatta*)
Ishikawa et al.[189]	Ph	M rat
Russchen[342]	HRP (col)	cat

(Table III continued)

Study	*Technique*	*Animals*
Luiten et al.[242]	HRP	M rat
Loughlin and Fallon[238]	Col	rat
Reep and Winans[333]	AA^+, HRP	M hamster
Fallon and Loughlin[113]	Col	M and F rat
Swanson[386]	Col/IR	M rat
Pascuzzo and Skeen[309]	HRP	cat
1983		
Macrides and Davis[245]	IR	M hamster
Loughlin and Fallon[239]	HF, AA^+	rat
Bagnoli and Burkhalter[19]	HRP	M and F pigeons
Felten and Sladek[124]	HF (Golgi/EM)	monkeys (*S. sciureus*)
Albanese and Minciacchi[6]	Col/HF	M rat
Fallon et al.[120]	HF/Col/IH	F rat
Pritzel and Markowitsch[329]	IR	lesser bush baby (*Galago senegalensis*)
Pearson et al.[313]	IR	human
1984		
Schwerdtfeger[354]	HRP	tree shrew (*Tupaia*)
Levett et al.[222,223]	HF	M *M. mulatta*
Tork et al.[408]	HRP/AA^+	M and F cat
Sobel and Corbett[374]	HF/Col	rat
Skagerberg et al.[369]	HF	F rat
Lindvall et al.[234]	HF	F rat
Fallon et al.[119]	HF/Col	F rat
Loughlin and Fallon[240]	HRP/HF	rat
Sarter and Markowitsch[349]	HF	rat
Studies in lower vertebrates		
Pisces: Lefranc et al.[221] (*Anquilla*)		
Baumgarten[29] (cyclostomes)		
Santer[346] (fish)		
Watson[428] (*Myoxocephalus scorpius*, teleost)		
Parent et al.[308] (*Lepomis gibbosus*, teleost)		
Parent and Northcutt[307] (*Lepisosteus osseus*, holostei)		
Yamamoto et al.[439] (teleosts)		
Amphibia: Parent[305] (*Rana pipiens*, frog)		
Dube and Parent[105] (*Necturus maculosus*, salamander)		
Reptilia: Parent[306] (*Chrysemys picta*, turtle)		
Wolters et al.[435] (*Varanus exanthemateeus*, lizard)		
(and other reports cited therein)		

jections to the preoptic area with HRP and fluorescent techniques and not found them[55,90,201]. More detailed study would be of value here, considering that these play an important role in controlling ingestive and reproductive behavior which are functions often impaired after large or laterally situated VTA lesions. A recent detailed study using wheat germ agglutinin and HRP tracers has confirmed reciprocal connections with the medial preoptic area[74]. The connection with the supraoptic nucleus would be of interest, if confirmed, as this area is known to be rich in DA and to be involved in controlling endocrinological function.

The median eminence contains high levels of DA, that are usually assumed to be tuberoinfundibular in origin. But DA levels were found to fall by 40% following VTA damage[208]. Further corroboration and detail of these putative projections are required. This pathway could provide one way for VTA activity to influence both hormonal secretion from the hypophysis and, thus, perhaps cognitive function in the limbic cortices.

Fibers ascend to the anterodorsal thalamic nucleus. Some of these are likely to belong to the acetylcholinesterase containing ventral tegmental tract described by Shute and Lewis[361]. The medial zone of

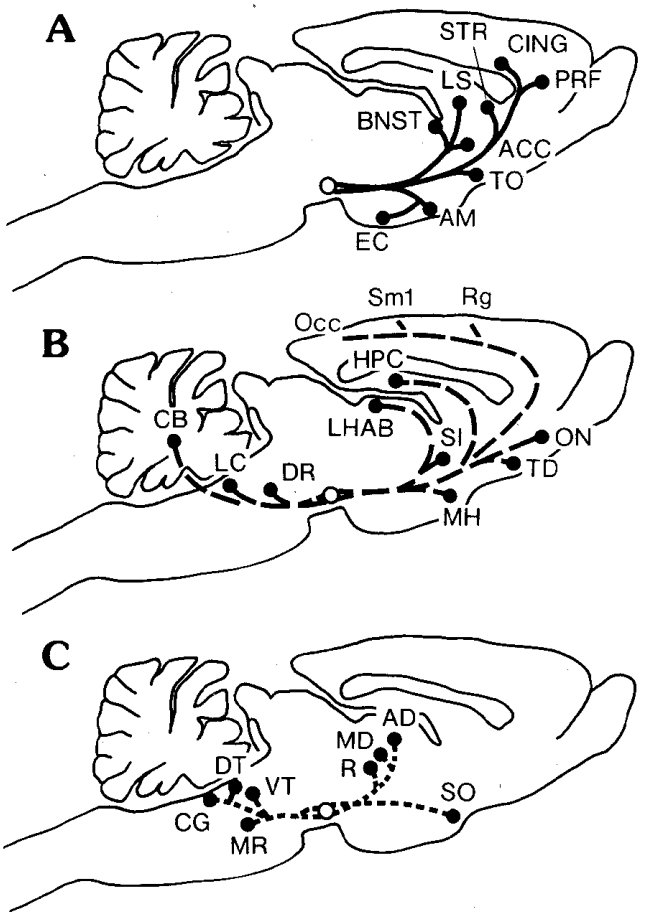

Fig. 7. General schematic representation of the main projections of VTA cells to regions rich in DA terminals (A), to regions with sparse DA terminals (B) and to areas that probably do not contain DA terminals (C) (Simon[362]). ACC, N. accumbens; AD, anterodorsal thalamus; AM, amygdala; CG, central gray; CING, cingulate cortex; DR, dorsal raphe; DT/VT, dorsal/ventral tegmental nucleus of Gudden; EC, entorhinal cortex; HPC, hippocampus; LC, locus coeruleus; LHAB, lateral habenula; LS, lateral septum; MD, mediodorsal thalamus; MH, medial hypothalamus; MR, median raphe; Occ, occipital cortex; ON, olfactory nuclei; PRF, prefrontal cortex; R, N. reuniens; Rg, retrosplenial granular cortex; SI, substantia innominata; Sm1, first somatosensory cortex; STR, neostriatum; SO, supraoptic nucleus; TD, diagonal band of Broca; TO, tuberculum olfactorium.

the mediodorsal nucleus, the N. centralis medius and the N. reuniens are also in receipt of projections from the VTA. The lateral habenula receives a major and possibly the medial habenula a minor projection from the VTA through the fasciculus retroflexus[318, 319]. The projection of the DA component (20–30%) centers on the caudomedial part of the lateral habenula[369]. VTA lesion results in ca. 75% depletion of DA in this nucleus[208].

For comparison, it is noteworthy that the N. interpeduncularis, ventral and posterior to the VTA, has strong reciprocal connections with the habenula and mediodorsal thalamus[265,420]. To a lesser extent the SN also projects to these nuclei — but to another subdivision of the mediodorsal thalamus[32].

When one considers the importance of the thalamic nuclei for modulating both cortical and subcortical function it is surprising how little attention either the VTA innervation of or the intrinsic DA connections within the thalamus have received 20 years after their discovery. (DA containing cells are found in the N. arcuatus, N. periventricularis anterior (A12), N. hypothalamicus posterior, area supramammillaris and N. reuniens thalami (A11)[87].)

No connections between the A10 and the subthalamic nucleus have been reported. This contrasts with the SN[260]. (It is assumed that the cholinesterase containing cells reported to project to the subthalamus and globus pallidus have their origin in the SN[361].)

2.2.4. *The mesostriatal pathway.* Innervation of the corpus striatum is densest ventroanteriorly and diminishes dorsally. VTA innervation is absent in the most medial, dorsal and laterocaudal striatum. The ventromedial VTA innervates the anteromedial striatum and the dorsolateral VTA the ventrocaudal striatum[418]. After VTA 6-OHDA lesion anterior striatal DA levels may drop by 70%[289a], at least twice the depletion seen in caudal areas (cf. a value of 80% striatal DA of nigral origin[103]; Fig. 8).

2.2.5. *The mesolimbic pathway.* Following several reports on the existence of DA in the lateral, but not in the medial septum of rats during the course of 1974, Segal and Landis[357] managed to confirm that the origins of these terminals lay with the cell bodies of the anterior VTA.

A very few fibers are found in the rostrodorsal part of the medial septum of rats. In the cat the density of the more medial projection is far higher[408]. But in other animals most projections terminate in the medial and ventral parts of the lateral septum (Table IV). Four separate if somewhat dispersed populations have been described[135]. In the medial part of the lateral nucleus DA containing fibers form a fine peripheral outline to the fornix[230]. VTA 6-OHDA lesions deplete the septal DA by 90%[289].

The first report of a mesolimbic projection was to the neighboring accumbens. It is perhaps the largest mesolimbic projection. It spreads through the ac-

cumbens, the tuberculum olfactorium and the bed nucleus of the stria terminalis.

Chronister et al.[76] reported a patchy distribution of terminals close to the lateral ventricle in the dorsocaudal part of the accumbens. Rostrally they found that the distribution spread to occupy the whole extent of the nucleus. The DA innervation avoids cell clusters rich in opioid peptides[171] (cf. striatum). In the region of the bed nucleus (N. interstitialis) the densest innervation was found in the dorsal half[229]. Projections to the accumbens and lobus parolfactorius have also been reported for the chicken[104]. Using 6-OHDA lesions of the VTA in the rat DA is depleted in the accumbens by ca. 85–95%[289,365]. Levels of DA reported for the accumbens of rat and man are similar — ca. 25–40 ng/mg protein.

With respect to the amygdala fibers have been traced to the N. centralis, N. lateralis anterior and posterior, N. medialis and N. basalis. Denser aggregations of DA fibers and terminals are found in the central, basolateral and intercalated nuclei than in the anterior basomedial and posterolateral areas[112].

It is important to note that both nigral (A9) and even thalamic (A11) cell groups project to the amygdala[71,112,299]. But it has been disputed whether the central nucleus, which contains the highest levels of DA in the amygdala, does in fact receive a non-DA A10 innervation[283]. Projections to the amygdala have also been reported for the N. peripeduncularis and interpeduncularis (rat, cat, monkey[259,298]). DA levels found in man range from 0.4 to 0.9 ng/mg protein. These are about a fifth of those found in the rat. VTA 6-OHDA lesions reduce DA levels in the amygdala by ca. 90% (Oades, in preparation.)

Rostral to the amygdala there are minor, but undisputed projections in the neighborhood of the accumbens off into the substantia innominata (ventral pallidum) and on to the N. tractus diagonalis. Jones et al.[195] also saw projections of peripeduncular origin in the monkey. In the human substantia innominata DA levels were found to be only marginally lower than in the amygdala (0.73 ng/mg protein) and homovanillic acid (HVA) levels were nearly 3 times higher (32.7 ng/mg protein)[10]. Even further rostrally in the ventral olfactory forebrain there are projections to the medial, lateral and dorsal olfactory nuclei.

2.2.6. *The hippocampal connection — a special case.* Evidence for a minor DA projection to the hip-

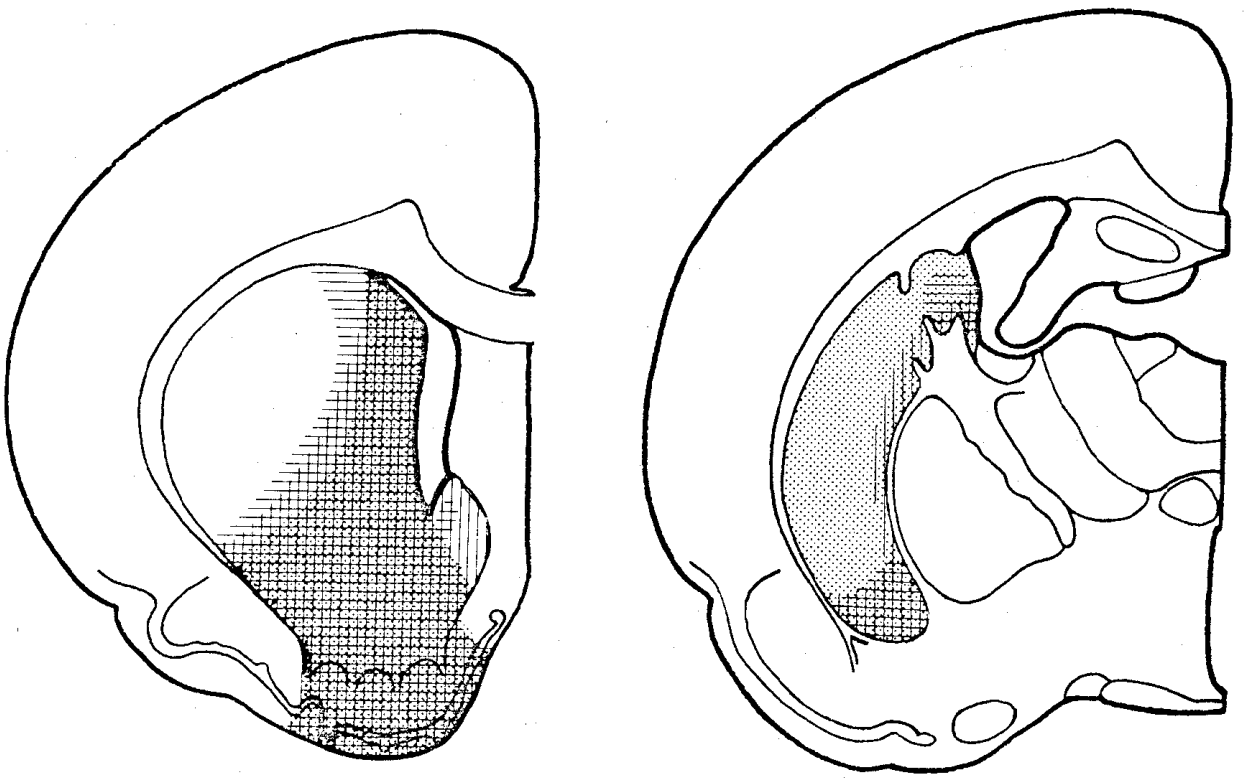

Fig. 8. Representations of the projections to the neostriatum (rostral and caudal sections) from the VTA (vertical lines), amygdala (stipple) and prefrontal cortex (horizontal lines). Local clustered distribution patterns are not shown. Overlap is most marked in anterior, midline and ventral regions (Kelley et al.[205,206]).

TABLE IV

Anatomical studies of the telencephalic and diencephalic projections of the VTA (A10) over 20 years after Dahlstrom and Fuxe[87]

Brain region	*Nucleus*	*References*
Diencephalon		
Hypothalamus	Dorso- and ventromedial (arcuate), supraoptic,	Simon et al.[364,368], Shen and Anderson[358], (Barone et al.[25])
	(medial) and lateral preoptic posterior	Beckstead et al.[32], Simon et al.[364,368], Luiten and Room[241], Barone et al.[26,27], Tork et al.[408], (Lindvall et al.[234])
Thalamus	N. anterodorsalis,	Simon et al.[364,368]
	N. mediodorsalis, centromedialis and reuniens	Guillery[153], Herkenham and Nauta[169], Rinvik[337], Carpenter et al.[70], Clavier et al.[78], Beckstead et al.[32], Simon et al.[364,368] Arikuni and Gotoh[13], Velayos and Reinoso-Suarez[420]
	Lateral habenula	Guillery[153], Jacobowitz and Palkovits[192], Lindvall et al.[235], Kizer et al.[208], Hökfelt et al.[179], Beckstead et al.[32], Herkenham and Nauta[169], Simon et al.[364,368], Phillipson and Griffith[318], Phillipson and Pycock[319], Albanese and Minciacchi[6], Lindvall et al.[234], Tork et al.[408], Skageberg et al.[369]
	Medial habenula	Phillipson and Pycock[319]
Median eminence		Kizer et al.[208], Simon et al.[364,368]
Telencephalon		
Striatum	Ventro-antero-medial,	Llamas and Reinoso-Suarez[236], Koob et al.[213], Simon et al.[364,367,368], Pasquier et al.[311], Fallon and Moore[115], Beckstead et al.[32], Pearson et al.[312], Haglund et al.[157], Szabo[393,394], Chronister et al.[76], Fallon et al.[120], Altar et al.[7], Tork et al.[408], Van der Kooy et al.[415], Veening et al.[418], Loughlin and Fallon[238], Fallon and Loughlin[113], Swanson[386], Albanese and Minciacchi[6], Tork et al.[408]
Olfactory tubercle, accumbens and nuclei of the stria terminalis		Fuxe[127], Anden et al.[9], Ungerstedt[412], Nobin and Bjorklund[284], Lindvall and Bjorklund[229], Fuxe et al.[131], Simon et al.[364,366–368], Koob et al.[213], Carter and Fibiger[71], Pasquier et al.[311], Fallon and Moore[114,115], Lindvall and Stenevi[231], Berger et al.[37], Nauta et al.[279], Haglund et al.[157], Gilad and Reis[143], Beckstead et al.[32], Szabo[393,394], Groenewegen et al.[150], Chronister et al.[76], Wang[427], Newman and Winans[280,281], Fallon and Loughlin[113], Swanson[386], Albanese and Minciacchi[6], Tork et al.[408]
Nuclei of the substantia innominata and tractus diagonalis		Fuxe[127], Lindvall et al.[232], Fallon and Moore[114], Lindvall and Stenevi[231], Beckstead et al.[32], Simon et al.[364,368], Tork et al. 1984[408]
Olfactory nuclei		Lindvall and Bjorklund[229], Fallon and Moore[114], Simon et al.[364,368], Davis and Macrides[88], Davis et al.[89]
Amygdala	N. centralis, lateralis (post. and ant.), basalis, medialis, lateralis	Fuxe[127], Anden et al.[9], Ungerstedt[412], Fuxe et al.[131], Hökfelt et al.[176–178], Lindvall and Bjorklund[229], Brownstein et al.[75], Ben-Ari et al.[33], Ottersen and Ben-Ari[299], Fallon et al.[117], Beckstead et al.[32], Simon et al.[364,368], Russchen and Lohman[343], Ottersen[298], Nitecka et al.[283], Mehler[259], Fallon[111,112], Russchen[342], Fallon and Loughlin[113], Swanson[386], Loughlin and Fallon[239], Lindvall et al.[234]
Septum	Lateralis	(Brownstein et al.[65], Lidbrink et al.[227], Lindvall and Bjorklund[229], Kopin et al.[214], Kizer et al.[208]), Fuxe et al.[131], Lindvall[228], Assaf and Miller[15], Carter and Fibiger[71], Bjorklund and Lindvall[51], Fallon and Moore[115], Lindvall and Stenevi[231], Haglund et al.[157], Beckstead et al.[32], Simon et al.[364,367,368], Krayniak et al.[216,217], Luiten et al.[242], Fallon and Loughlin[113], Swanson[386], Albanese and Miniciacchi[6], Tork et al.[408]
Hippocampus		(Swanson and Hartman[390], Hökfelt et al.[176–178], Smialowski[371], Storm-Mathisen[381], Smialowski et al.[372], Dolphin and Bockaert[101], Bishoff et al.[48,49], Herrling[172], Ishikawa et al.[189]), Cragg[84], Schwab et al.[353], Simon et al.[364,368], Wyss et al.[437], Amaral and Cowan[8], Scatton et al.[351], Schwerdtfeger[354], Swanson[386], Lindvall et al.[234]
Transition and Neocortices		(Thierry et al.[404,405], Hökfelt et al.[176–178], Berger et al.[39,40], Lindvall and Bjorklund[229], Fuxe et al.[131,132], Kizer et al.[208])
	Entorhinal (v/l)	Lindvall et al.[235], Carter and Fibiger[71], Fallon et al.[117], Haglund et al.[157], Beckstead et al.[32], Simon et al.[364,368], Beckstead[31], Collier and Routtenberg[79], Swanson[386], Lindvall et al.[234], Loughlin and Fallon[240]
	Cingulate (ant.)	(Lindvall et al.[232], Lewis et al.[224]), Emson and Koob[108], Lindvall et al.[233], Divac et al.[98], Simon et al.[364,368], Beckstead et al.[32], Markowitsch and Irle[252], Swanson[386], Porrino and Goldman-Rakic[326], Felten and Sladek[124], Pritzel and Markowitsch[329], Loughlin and Fallon[240], Tork et al.[408]

(Table IV continued)

Brain region	*Nucleus*	*References*
	Suprarhinal/insular	Fallon et al.[117], Fallon and Moore[114,115], Lindvall et al.[233], Divac et al.[98], Simon et al.[364,368], Beckstead et al.[32], Tork et al.[408], Sobel and Corbett[374]
	Prefrontal (antero-medial in rat)	(Brown and Goldman[64], Lindvall et al.[232]), Lindvall and Bjorklund[229], Lindvall et al.[235,233], Beckstead[30], Llamas et al.[237], Carter and Fibiger[71], Emson and Koob[108], Divac et al.[98], Beckstead et al.[32], Simon et al.[364,367,369], Haglund et al.[157], Markowitsch and Irle[252], Albanese and Bentivoglio[5], Porrino and Goldman-Rakic[326], Fallon and Loughlin[113], Swanson[386], Pascuzzo and Skeen[309], Felten and Sladek[124], Albanese and Minciacchi[6], Pritzel and Markowitsch[329], Sarter and Markowitsch[349], Loughlin and Fallon[240], Tork et al.[408], Sobel and Corbett[374], Fallon et al.[119], Levitt et al.[222,223]

pocampus from the VTA has grown up piecemeal over 10 years. In view of the controversy this evidence generated, the mesohippocampal connection is treated separately and in detail. It is salutary to note that there are interpeduncular connections to the septum, posterior hippocampus and entorhinal cortex[359] in rats[20] and in cats[380].

Hökfelt et al.[176–178] first speculated that some of the catecholaminergic fluorescence that they observed in the hippocampus could reflect the presence of DA. Swanson and Hartman[390] noted that the distribution of NA and the catecholamine synthesizing enzyme dopamine β-hydroxylase did not always match. In 1976 Hamilton and Mackay[163] reported that lesion of NA pathways reduced hippocampal levels of DA proportionately far less than they did levels of NA. In the same year Smialowski[371] reported that apomorphine (DA agonist) and DA, but not NA, had a stimulatory effect on the EEG recorded from the hippocampus. Certainly this could easily have been an indirect effect. Nonetheless in 1977 Storm-Mathisen[381] noted that some of the fibers he observed fluorescing in the hippocampus could contain DA.

By the end of the seventies a small number of apomorphine[372] and spiroperidol binding sites had been found[300]. Indeed the presence of a DA-sensitive adenylate cyclase that could be blocked with the neuroleptic fluphenazine[100,101] or micromolar haloperidol has been reported[24]. Stimulation of DA-sensitive adenylate cyclase, if not very impressive[110] is present[24].

There is further pharmacological and neurophysiological evidence for DA activity in hippocampal neurons. The application of DA on to the hippocampus depressed levels of spontaneous firing and that elicited by glutamate[48–50,172,356]. Intracellular recording from the hippocampal slice has shown that DA exerts specific effects distinct from those of other transmitters. Action potentials recorded from CA_1 pyramidal cells repolarize to a more negative potential[322]. Other effects include a hyperpolarization dependent on a calcium-activated increase of potassium conductance. This effect was blocked by the partial D_1 antagonist α-flupenthixol[46,47]. It should be cautioned that the neuroleptic fluphenazine has been observed to antagonize neurophysiological responses of the hippocampus to NA[302]. However, in the hippocampal slice DA and apomorphine in low doses reduce the outflow of labelled NA by way of a DA agonist/antagonist-sensitive mechanism[190]. Further indirect evidence also comes from EEG records. The neuroleptic chlorpromazine modulates ϑ-rhythms[133].

What about more direct measures of DA activity? Haloperidol increased whereas apomorphine decreased the rate of formation of the DA metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in the hippocampus[48,49]. Ishikawa et al.[189] reported that levels of DA sensitive to treatment with haloperidol, were distributed more dorsally than ventrally in the hippocampus by a factor of 4–10 (Table V).

Precisely in this dorsal area Martres et al.[257] reported a high density of labelled iodosulpiride in the rat. These ligand sites were specific to the stratum lacunosum moleculare and decreased in density from the CA_1 to the CA_3 (also cf. ref. 42 for DA-sensitive receptors in the rat hippocampus). Thus reports of a functional DA presence persisted despite many dismissive reports that very little DA[183] and exceedingly few DA receptors were present[67,226,373]. Strittmatter et al.[383] demonstrated the presence of presynaptic DA receptors controlling acetylcholine outflow in the hippocampal slice (rabbit). But they questioned

TABLE V

Examples of reports of the concentration, activity and binding of dopamine in the hippocampus

	DA		*DOPAC*	*DOPAC/DA*	*Spiperone*	*Source*
	ng/mg prot.	*ng/g wet wt.*	*ng/g wet wt.*	*utilization*	*binding mol/mg prot.*	
Rat					120	List and Seeman[235b]
					15	Bischoff cit. Dooley and Bittiger[102a]
		0.60				Westerink and Mulder cit. Dooley and Bittiger[102a]
		14	8.2	0.586		Bischoff et al.[48]
		52	34	0.654		Ishikawa et al.[189]
		13				Archer et al.[11]
		0.022				Lindvall et al.[234]
		212		(0.138 g/g/h)		Lasley et al.[220] (label-precursor-TR method)
			3.21			Westerink et al.[430]
		27.5	23.2	0.844		Oades et al.[289a]
		24	54	2.25		Ikarashi and Maruyama[187]
	108					Bjorklund et al.[54]
	1.6					Van Heuven-Nolsen et al.[416]
Rabbit	16					Strittmatter et al.[383]

	HVA		*DOPAC/DA utilization*	
	ng/mg prot.	*ng/g wet wt.*		
Monkey (*Apus cebella*)	0.58 ng/mm^3			Haggstrom et al.[156]
Human		161	2.52	Adolfsson et al.[1]
	8.8		0.63	Scatton et al.[350a]
		356	25.6	
	10.5	356	0.79	Scatton et al.[352]
	5.07			Arai et al.[10]
0.18				Ploska et al.[321]

whether these sites were of physiological significance. Further Westerink et al.[430] suggested that the very rapid removal of DA in the hippocampus was an argument against a transmission role or a special storage compartment for DA. Nevertheless a recent study of protein phosphorylation in subcellular fractions and synaptic plasma membrane fractions makes a convincing case for the process being dependent on the concentration of DA[197]. They argue for a DA receptor-mediated effect.

To return to anatomical studies, Benowitz and Karten[34] had, largely unnoticed, described the projection of the tractus infundibuli in the pigeon from its origin in the Nln caudalis to the parahippocampal area. Rather unexpectedly they have argued that this area may be the avian equivalent of the mammalian subiculum.

Simon et al.[364] made the direct claim, on the basis of anterograde transport of tritiated leucine, that DA fibers from the VTA innervated the internal edge of the hilus of the gyrus dentatus. The effect of VTA lesions suggests that whereas the A10 neurons innervate both the anterior and posterior regions of the hippocampus, A9 neurons (after SN lesion) are seen to contribute only to the more posterior innervation[351]. (The possibility of the A9 innervation was suspected earlier from behavioral observations after unilateral SN lesion and hippocampal stimulation with NA[285].)

Studies with HRP and wheat germ agglutinin have confirmed the VTA–hippocampal projection in the rat[353,437] (not[323]), in *Tupaia*[354] and in *Cynomolgus* monkeys[8].

Swanson[386] injected True blue into the CA_1, CA_3

and dentate gyrus of rats. The rostral two-thirds of the VTA was labelled. He also reported that the connection was crossed (20%). By contrast the projection from the SN was uncrossed. He estimated that both VTA and SN projections consisted of about 6% DA fibers. However, this investigation was restricted to the septal pole of the hippocampus. Verney et al.[422] have reported a very thorough survey of the DA projection using immunocytochemical and histofluorescent techniques in combination with NA and DA neurotoxins. They found a predominantly ventral distribution of DA terminals in the molecular layer of the prosubiculum and the stratum oriens of CA_1. A very few terminals were seen in the polymorphic layer of the dorsal subiculum and down to the granular layer of the dentate gyrus. (They explain the reason why Jonsson et al.[196], and others (above), found higher levels of DA dorsally: the dissection was different and their dorsal region included DA fibers of passage.)

Thus in birds and throughout the mammalian series there appears to be a VTA–hippocampal pathway. In contrast to the opinion of Farley et al.[121], there is no evidence that the DA innervation has become reduced in man. In their analysis DA levels (<30 ng/g) were at the limit of detectability. The French group performed a finer analysis of the rat hippocampus[351]. They were only able to report a level of 10 ng/g (i.e. below the detectable limit for Farley). The French figure corresponds to that obtained by Ishikawa et al.[189]. But it is interesting that in this latter study a restricted part of the middorsal hippocampus contained 10 times this amount. In the avian hippocampus the DA:NA ratio is 0.54 (ref. 97). From the above studies in the rat it is 0.3 and in man 1.1 (Table V).

In man it is the ventral hippocampus that is significantly developed[421] — precisely that part which is in receipt of the DA projection. Levels of DA in the human hippocampus approach or surpass those of the entorhinal or prefrontal cortices[164,352].

2.2.7. *Pathways to the rat cortices.* The VTA projections to the transitional and neocortices are discussed to illustrate both the development of present ideas as well as certain points of controversy.

It was not until Thierry et al. in France[404,405] demonstrated the synthesis of DA from labelled tyrosine in the cortex that the existence of DA, not just as a precursor to NA, but as a neurotransmitter, was seriously considered. It was soon confirmed that there is a high concentration of DA and DA containing terminals in the anterior cingulate cortex, the (pre)piriform/suprarhinal, claustrum, entorhinal and prefrontal cortices (Table IV, in parentheses). Recently immunocytochemical data have indicated a more extensive innervation[41].

Since 1974 there have been disagreements over the extent of the frontal-perirhinal innervation and whether the anterior cingulate cortex is innervated by the A9 and/or the A10.

Most authors agree that there is an A10, as well as an A9, innervation of the ventrolateral entorhinal cortex. Most of the DA terminals are found in clusters in layers II and III[230]. In the rat DA concentrations of 3.8–4.5 ng/mg protein[416] or 54 ng/g wet wt.[11] have been reported. Proceeding on into the amygdaloid/piriform area a 4-fold increase has been reported[234].

Lindvall et al.[235] claimed that the cingulate cortex received a DA projection from the lateral part of the A9. They provided no description of the lesion, thus their claim is difficult to assess. In the mid-seventies projections to the cingulate from the medial SN pars compacta were reported[30,71]. However, a sensitive radiochemical assay has since shown that whereas A9 cells innervate the superficial layers (I–III), the A10 additionally innervates the deeper layers[108]. The stronger DA innervation is usually to the superficial layers[224].

Although authors vary in where they draw the border between the caudal extension of the anteromedial and the rostral extension of the cingulate cortex in the pre/supragenual region in rodents, a dual innervation of this area has been confirmed by various methods[32,233,252,264]. In the rat 55 ng/g wet wt. have been reported for this region.

There is no disagreement that in the pregenual region of rodents, the prefrontal anteromedial cortex receives projections from DA containing cells of the A10 and A9 (Table IV). The rostrocaudal pre/supragenual continuum of DA-innervated cortex has an impressive 5 mm length in the rat[400,401]. It is precisely this area that also receives a projection from the mediodorsal thalamus, that is used to 'define' the prefrontal cortex[233]. DA levels vary enormously from study to study (75–375 ng/g wet wt., usual range 70 to

125 ng/g wet wt., 0.6–2.0 ng/mg protein (25–60% of NA levels)[11,22,289,292]). The DA turnover is higher here than in other projection areas[400,401] (DOPAC, 30–100 ng/g wet wt., 0.28–0.65 ng/mg protein; HVA, 30–90 mg/g wet wt.). Utilization is double that in mesostriatal or mesolimbic systems[22].

There is also a more laterally situated projection area around the rhinal sulcus. This was originally described as lying within the sulcus[235] and later dorsal to the sulcus[39]. The area concerned covers the transition between the neocortex and the piriform cortex. The perirhinal projection area is referred to in some studies as suprarhinal and in others as piriform cortex — the length of the innervated area varying between studies. (Swanson preferred to say that strictly speaking there was no projection to 'piriform' cortex[386].) Cytoarchitectonically this area may be best considered related to that of the insular cortex of subprimates[154]. Part of this area has also been considered homologous with the caudal orbitofrontal cortex of monkeys (discussion[39]). Considering that both sulcal and dorsomedial cortices receive a specific innervation from the mediodorsal thalamus, both areas may be considered as prefrontal cortex.

There is some evidence that the left anteromedial but not the left insular contains more DA than the right[370]. Although this was not recorded in the study of Robinson et al.[339], a high level of glucose utilization has been noted in the same area on the left side[144].

Early anatomical evidence for a sparse distribution of DA fibers in the rat through the dorsal and lateral cortex[233] was not confirmed pharmacologically[370].

In view of the close functional and anatomical connections of the parietal and VTA-innervated cortices, the absence of reports of VTA projections to the former is surprising. In both the rat and cat total CA content is twice that considered to represent precursor levels for NA synthesis (59–97 ng/g[204]; 144 ng/g[332]). Striatal levels of NA or hippocampal levels of DA are of the same order as the report of Brownstein et al.[65] of 1.3 ng/mg protein parietal DA. The content[344], the binding levels of DA[250] and ^{125}I-sulpiride[257] in the parietal cortex are higher than in occipital areas, although, with the latter ligand levels are but 3% of those in the neostriatum[257a].

More recently an immunocytochemical study[41] of the distribution of TOH following depletion of NA (neonatal 6-OHDA, DSP-4) provided unequivocal evidence of a more widely distributed cortical innervation by DA which is likely to be shown to be more highly developed further along the phylogenetic scale. A band of low density innervation was recorded for granular and agranular cortex in a band from the anterior part of the visual cortex (area 18b) over retrosplenial loci (area 29b–d) to a lateral region of the primary motor cortex which shows some parallels with the primate supplemental motor area. Staining was largely restricted to laminae I–III. Many of these areas have not yet been the subject of retrograde tracing studies. Confirmation of a VTA origin for a part, but not all of this innervation might be expected.

2.2.8. *Species variation in the mesocortical projection.* Two factors should be borne in mind when one considers more recent studies that have started to look at other animals. Firstly the techniques have become more refined (e.g. fluorescent dyes, BDHC vs DAB–HRP-treated material[53,262]). This means that non-rat material is being looked at for the first time with techniques more refined than those often used with rats. Secondly, one must consider that some connections may be discovered that reflect a specific specialization or an evolutionary trend. (An example of the former may be the claim that the insular cortex of hamsters is innervated more by A11 than A10 neurons[333].)

Most studies show an impressive similarity for the pattern of innervation shown by the VTA of most subcortical areas. But there is a broader innervation of the association cortices in carnivores and primates.

Let us take the cat as representative of the carnivores. Tork and his colleagues[352a,352b,407,408], report that at least 12 cortical areas receive innervation from the VTA. These include sensory (auditory, visual and somatosensory), motor and limbic areas (retrosplenial, cingulate and entorhinal). The strongest innervation was shown by prefrontal, insular, cingulate and visual cortices. Other authors have noted a particular VTA innervation of visual areas[35], the sylvian, medial sylvian, posteroventral temporal[252], ectosylvian and sigmoid areas[16,36,237,252,408]. Another marked difference from the rat, where both A9 and A10 cells project to the cortices, is that only A10 cells of the cat show cortical projections[352a,352b]. However, this may well represent a divergence peculiar to car-

nivores as both A9 and A10 cells project to the cortices of primates[326].

Some systems, clearly marked in the rat, are well represented in the cat (e.g. prefrontal/gyrus proreus). Other projections to poorly circumscribed areas of the rat (e.g. retrosplenial cortex[32]) are expanded in the cat[194,252,352a,352b]. Innervation of other association cortices in cats may represent an expansion of systems very poorly represented in rats[233], rather than a topographical departure from the principle and localized innervation of the anteromedial and sulcal cortices in the rat.

Could the sensory cortical projections represent a group specialization? Another peculiarity of the visual system in cats is the projection of the lateral geniculate nucleus to cortices outside area 17 (ref. 44). So VTA projections to occipital[408] as well as frontal eye fields[309] seem less unexpected. Nonetheless the use of sensitive immunocytochemical techniques indicates that a visual cortical projection in cats may be the continuation of an evolutionary feature from rodents[41] that becomes more pronounced in primates (see below).

Lower primates, such as the bushbaby, may represent a half-way house to the true primates. In this case projections are reported to dorso- and ventromedial frontal and cingulate rather than lateral cortices. Other cortices receive but minor projections[329]. Even here one should not lose sight of the possibility of species-specific differences until studies with more sensitive techniques are undertaken. For example Divac et al.[98] were unable to record the superficial DA innervation of the cingulate cortex in either the opossum or tree shrew.

A series of anatomical and pharmacological studies with rhesus monkeys[64,222–224] confirmed DA projections to dorsolateral (Brodman area 9), orbital (10–14) frontal and cingulate (24) cortices as well as the anterior superior and inferior temporal gyri (20–22, 41). Here DA and NA fibers have been observed 'densely intertwined'. DA levels ranged from 50 to 70% of the NA present. (cf. DA/NA ratio in the prefrontal cortex (PRF); rat, 0.4; bird, 1.0; man, 0.5 (refs. 11, 97, 331, 352).)

In biochemical studies absolute measures of DA and its metabolites (DOPAC, HVA) may vary between studies by a factor of 5–10; thus the case for DA function as a transmitter in association cortices will be made by reference to prefrontal areas.

Through the primates there may be both quantitative and qualitative differences in the mesocortical projections with respect to rodents. On the quantitative side Bacopoulos et al.[18] noted that the levels of DA metabolites in the rat cortex are minute. In the rhesus monkey this proportion constitutes 20–40% of the total. On the qualitative side there is evidence for differences with respect to rodent systems that are at least as marked as those shown by carnivores. Unfortunately, for the most part, the evidence is pharmacological and thus indirect.

In the adult rhesus monkey the proportion of HVA in the parietal cortex is 50–60% of that in frontal regions[17,146]. The earlier study[146] found values higher than parietal levels for the pre- and postcentral superior and inferior temporal, premotor (6) and motor (4) cortices. In *Cebus* monkeys temporal HVA levels were 80% of those in the frontal cortex[156]. By contrast levels in the occipital cortex of rhesus seemed to be but a third of parietal values for DA and HVA.

Measures of levels of DA in the cortices of man tell a similar story. Values for temporal and frontal cortices are similar[142,345]. In the parietal cortex levels were 43%[1], 63%[345] or 130%[142] those in frontal areas. (The differences reflect sampling. Thus the inferior frontal gyrus contains but one sixth of levels in the midfrontal gyrus[38].) Occipital values were around 60%.

What is the relationship between DA and HVA in these areas? DA utilization can be estimated from data of Adolfsson et al.[1]. The HVA/DA ratio[341] for frontal cortex is 0.57, parietal cortex is 2.9, temporal cortex 2.6 and occipital cortex is 1.8. The frontal values are comparable to frontal DOPAC/DA ratios in rodents. Lest the other values should appear exceptional, the same study found values of 2.2 for the caudate and 4.9 for the putamen in man (n, 18)[1].

On following the changeover through the transitional entorhinal to archicortical amygdala there seems from some recent biochemical studies to be a relative drop in the DA innervation to levels less than those found in the rat on a weight to weight basis[10,321,352].

It seems important to point out that future anatomical work should consist of retrograde studies of as much material as possible in order to test the 'indications' gained from pharmacological studies. Large

areas of the cortices have never been investigated after injection of tracers. The conventional tendency to select one in so many sections should be resisted, despite the mountain of work! Unpublished results of immunocytochemical studies of tyrosine hydroxylase (TOH) clearly show a more widespread DA innervation than previous anatomical methods have shown — more than fulfilling the predictions from neurochemical analyses. Finally it must be emphasized that non-DA projections of the VTA to the cortices undoubtedly exist. Neither pharmacological nor anatomical methods have been applied to examine this issue in detail. In rodents only one third of mesocortical fibers are estimated to contain DA[120,386].

2.2.9. *Cortical DA terminal distribution.* Four sources of afferent input have been important, historically, for the classification of the frontal cortices and naturally are important determinants of function[332a]. Layer II receives amygdalofugal input, layers II and III hemispheric associational input and layer IV input from the thalamus.

In the pregenual frontal cortex some VTA DA terminals are found distributed from layers II to VI[235], but in all the studies cited in Table IV by far the greatest density was found in the deepest layers (V and VI). This pattern of innervation continues into the cingulate cortex. But in the cingulate of *Rhesus* a denser innervation was noted in layers II and III where NA proved largely absent[223]. In rodents and possibly in other groups a weak innervation of these laminae stretches out over the retrosplenial to the anterior visual cortex[41].

In the suprarhinal zone terminals are largely confined to layers V and VI[32,235]. A transition from the deep innervation in the suprarhinal area to a more superficial innervation has been observed with caudal progression into the piriform cortex[233]. In the entorhinal cortex terminal aggregations are reported to be particularly visible in layers II and III that also receive an input from the hippocampus[176,235,271]. However, Beckstead et al.[32] reported seeing some DA terminals in all layers. The hippocampal DA innervation, seen most intensely at the border between the prosubiculum and CA_1, also takes the form of islands (in the stratum moleculare and oriens, respectively) though they are somewhat smaller than in the entorhinal area[422].

For comparison NA fibers innervate layers I, IV and V and 5-HT fibers innervate all layers of the neocortex[223].

2.2.10. *Distribution of two types of fibers.* Careful observation of histofluorescent material has indicated that there are at least two types of efferent VTA DA fibers. The type 1 neuron is weakly fluorescent. It has a very fine axon. There are a large number of varicosities often obscuring any smooth segments of the axon in between. These fibers form dense pericellular terminal arrangements around non-fluorescing cells.

The type 2 neuron is strongly fluorescent which might reflect a high level of DA activity[2]. These neurons typically show smooth axons with very few varicosities. The terminals form small 'nest-like' arrangements on non-fluorescing cells[39,40,228,231,270,271].

In the lateral habenula[319] and lateral septum type 2 fibers are abundant — but type 1 fibers are also seen more medially in the lateral septum forming a band around the fornix[228,231,269,270]. Ontoniente et al.[297] distinguished such a varicose group of terminals in the ventroanterior septum from a pericellular innervation found more dorsally, extending throughout the rostrocaudal extent of the septum.

Both type 1 (ref. 270) and type 2 (ref. 231) fibers have been seen in the accumbens. Type 2 fibers are also reported for the tuberculum olfactorium and olfactory nuclei[271]. Both types have been seen in the amygdala, where type 1 is said to be more prominent in anterior planes[271].

In the pregenual frontal cortex the perirhinal and entorhinal cortices type 2 fibers predominate[39,40,233,271]. However, within the superficial layers of the supragenual limbic cortex and the band of innervation reaching the visual cortex are type 1 fibers[41,179,233]. By contrast in the deeper layers innervated by the VTA type 2 fibers are reported[39,271]. Confirming these observations on the cingulate cortex Lindvall and Bjorklund[230] remark that lesion of the SN consistently removes the fine, varicose supragenual terminal system.

2.2.11. *Uni- vs bilateral projections.* As a simple generalization the majority of ascending (and descending) connections of the VTA are ipsilateral. The point has been emphasized in studies conducted on rats with respect to striatal[76], amygdaloid[111] and other mesocorticolimbic structures[230,326]. However, during the early eighties an awareness grew of the ex-

TABLE VI

Selected mesolimbic and mesocortical projections in the rat: relative contribution of DA neurons, of crossed paths and their VTA origin (derived from Swanson[386])

Region	*% DA*	*% Crossed*	*Remarks on origin in VTA*
Prefrontal cortex	30–40	11	Cells widely distributed (more dorsal)
Cingulate cortex	25–35	12	Cells widely distributed (more ventral)
Entorhinal cortex	45–50	8	Cells ventrorostral to ventrocaudal
Hippocampus	ca. 6	21	More cells rostroventrally
Lateral septum	70–80	7+	Cells lateral and medial, more in rostro-mid-ventral areas
N. accumbens	80–85	8	Cells widely distributed
Lateral habenula	ca. 1(?)	8	Most cells medially
Amygdala	50–60	2	Most cells in ventral two thirds

tent to which a minority of fibers in different pathways were crossed.

In reviewing several studies from his laboratory Simon[362] pointed out in 1981 3 exceptions to the rule of unilaterality. He maintained that the LC, the anterodorsal thalamus and the olfactory nuclei received a bilateral innervation. Fallon and Moore[114] could find but a unilateral projection to the olfactory nuclei. But surprise reports soon claimed a restricted contralateral projection to the neostriatum[238,418] and the dorsal accumbens of rats and rabbits[76].

Evidence from a few studies in cats suggested that there was a tendency for the mediodorsal thalamus[420], neostriatum[408] and other forebrain areas[16] to receive minor contralateral projections. But Irle (personal communication, 1982) did not note any contralateral projections following unilateral injections of HRP. In 1982 Dube and Parent[105] saw some crossing of fibers in the anterior commissure of amphibia. This was taken to indicate that the phenomenon could be more widespread in non-mammalian species. In the absence of further reports from cats and primates it was not possible to comment on the possibility of a phylogenetic trend.

Since then the use of more refined tracing techniques has shown that for most structures 1–10% of projections are crossed. At first 1–2% of the mesostriatal projection became established as containing crossed DA and cholecystokinin fibers[7,120,122,238,254,418]. The crossed mesostriatal fibers derive from the Npbp and Npn[143a]. The general pattern was shown in a major study by Swanson[386] and has been confirmed in subsequent reports[6,352a,369]. Of the descending projections only those to the deep mesencephalic nucleus and the N. reticularis pontis oralis are exclusively ipsilateral[143a] (Table VI).

Perhaps, from a functional point of view a short cautionary remark is appropriate. Barone et al.[25–27] reported neurophysiological evidence from the medial hypothalamus for the possibility that VTA neurons can exert functional effects in the contralateral hemisphere. Many such effects, however, can be polysynaptically mediated. Some projection areas are bilaterally linked. This is well known for the association cortices, but is also true for other areas that are not widely known to project to each other across the commissures (e.g. striatostriatal projections[21]).

Nonetheless the comparatively unilateral projections of the VTA stand in contrast to those of other monoaminergic brainstem nuclei. Perhaps a few more neurons from the SN than the VTA have been noted to project bilaterally. But like the VTA such projections are to the diencephalon and basal ganglia[122,140].

2.2.12. *Collateral neural projections.* As long ago as the pioneering study by Ungerstedt[412] it had been suspected that some VTA cells had axon collaterals that innervated separate pairs of structures. But only with more recently developed techniques (e.g. double labelling with fluorescent dyes) have anatomists been able to provide evidence.

Initially on the basis of separate distribution patterns shown by separate labelling experiments, it was suggested that some neurons might dually innervate the striatum and cingulate gyrus, the septum and prefrontal cortex[230,232,235]. The central position of the septum has since been confirmed by Fallon[111,240] with double and triple labeling techniques and by French and Canadian neurophysiologists with electrical stimulation and recording techniques[93,248].

The fibers projecting to the septum may also innervate the prefrontal cortex (area 32), the striatum, the

accumbens and the lateral habenula. Double labelling has been recorded for accumbens, septum, entorhinal or sulcal cortex with medial prefrontal regions[374,386] and for accumbens or habenula with the two LC[386].

There is neurophysiological evidence for single neurons innervating both lateral hypothalamic and lateral preoptic regions[25–27], lateral hypothalamus and lateral habenula[266], the anterior hypothalamic complex and the accumbens[246], the lateral septum and amygdala[248].

In general the number of neurons showing collateral innervation is a small proportion of the total number of neurons present in the VTA, but extensive collateralization is reported in the recently discovered wideranging mesocortical innervation[352b].

Fallon[111] has even reported a few cases of triple labelling — e.g. striatum, septum and area 32. However, he emphasized that nigral cells send out more collaterals than those of the VTA and that in the VTA multilabelling was most often seen laterally in the Npn. His pioneering studies have shown that VTA neurons show fewer collateral connections than the SN, raphe or LC (respectively in quantitative order). In retrograde labelling studies the greatest overlap is seen after injections in the medial caudate, lateral septum, tuberculum olfactorium, accumbens, prefrontal cortex and amygdala. This illustrates where the potential for collateral innervation lies. This was found in a restricted zone in the dorsal Npn and ventral Npbp[113].

2.2.13. *Topography of the origins of VTA projections.* The refinement of fiber tracing techniques has only recently enabled a categorization of the projections of the VTA in terms of each constituent nucleus. Only one of the earlier studies showed a uniquely restricted source of innervation. The DA projection to the lateral habenula originates in the Nif and Npn[315,318]. However, the non-DA projection may emerge from any of the VTA nuclei[369]. Current studies show that there are gradients for the distribution of cells of origin of the different projections within each nucleus[386]. However, it seems inappropriate to consider these details at this stage until a number of studies are published and confirm the relationship between DA (and non-DA[175]) projections, their specific nuclei of origin and their cytoarchitecture. Further we believe it is more useful to provide a summary across the VTA as a basis for those studies that attempt to relate structure to function until the techniques for such study are refined enough to take account of the new anatomical precision.

The results of most studies support generalizations about crude topographic gradients along mediolateral, rostrocaudal and dorsoventral dimensions. Cells distributed more laterally in the VTA tend to project to more lateral structures; those found more rostrally tend to innervate the more rostral structures; the more dorsal cells usually project to the more ventral structures[271]. These trends should not obscure the heterogeneity of the VTA. It is apparent that, for example, some medially situated cells do project to the more lateral structures and some of the more lateral cells project to structures close to the midline. Fallon[111], following the injection of different dyes into the frontal cortex, septum and striatum, has made the striking observation of adjacent cells in the VTA, each containing a different dye.

Mediolateral topography. Medially situated VTA cells (e.g. Nln and Nif) project to the septum, the diagonal band, the bed nucleus of the stria terminalis and the pregenual cortex[32,51,71,157,201,230–232,357,364]. But there are reports of cells found in the ventromedial Npn and more lateral VTA projecting to the septum[15,111,201] and frontal cortex in the rat[130,157], if not the cat[352a,b]. The more lateral VTA fibers project to the suprarhinal cortex[31,39,229,232,233].

The division of opinion over whether the more lateral[30,130,232,233,235,364] or more medial[54,157,374] cells project to the cingulate cortex probably reflects the extent to which the two separate projections from A9 and A10 were affected by the experimental technique. Interestingly Porrino and Goldman-Rakic[326] found in the monkey, where part of the prefrontal cortex has migrated laterally, that the more medial VTA neurons projected to the ventral prefrontal cortex whereas the more lateral neurons projected to the dorsolateral prefrontal cortex (and cingulate).

Some authors report that more laterally placed cells project to the entorhinal cortex and amygdala[115,130,239,364]. Others found more medially situated cells of origin for these projections[32,51,157]. The detailed study of Fallon and Loughlin[113] noted a large projection to the amygdala from the Npbp, but that some cells throughout the A8–A10 continuum project to the amygdala.

Cells throughout the VTA project to the ventral striatum, accumbens and tuberculum olfactorium[32,71,157,201,279,364,394]. Some have suggested that the more lateral cells project to the anteromedial striatum and more medial ones to the accumbens[6,51,58,71,230,364,399] reflecting a more general point to point medial to lateral topography[394]. However, within the accumbens a more recent study of the rat has reported that whereas the Npbp projected mostly to the lateral parts, medial regions received projections from both the Npn and Nif[318a].

The more medial cells of the VTA are said to provide the projection to the hippocampus[351].

Electrophysiological studies have given rise to the suggestion that although non-DA projections can arise from the medial or lateral VTA[247,248], they are more common in the lateral part[427].

A certain mediolateral topography within the VTA reflects in miniature the projections from the A8–A10 continuum. Thus the more lateral SN cells project more laterally in a given structure than those of the VTA that project to the same structure[111].

Rostrocaudal topography. Both rostral and caudal neurons may contribute to a given VTA projection, but when they both contribute, they usually maintain their rostrocaudal relationship in the projection area. For example neurons along the entire rostrocaudal axis of the VTA project to the frontal cortex[233] but rostral cells project rostrally[71] and caudal cells project caudally in the medial prefrontal[364] and sulcal cortex[374].

There is a tendency for the more rostral cells to project to the septum[231,233,315,357] and more caudal cells to the entorhinal[71,271] and piriform cortex[364].

Dorsoventral topography. The more caudal cells of the VTA are also the more dorsal cells. For those areas projected upon from the entire rostrocaudal axis of the VTA, such as the prefrontal cortex, accumbens and neostriatum, there is a tendency for the more ventral parts to be innervated by the more dorsal cells and the more dorsal parts of the projection area to be innervated by the more ventral cells of the VTA[114,115,232,233,235,315,393,418].

Afferents to the suprarhinal cortex tend to come from the more dorsal cells in the VTA[232]. In addition projections to the septum tend to come from the more ventral cells[15,114,115,231,315].

In contrast to this simple dorsoventral distinction, Ottersen[298] found one target, the central nucleus of the amygdala of the cat, to receive projections from both the anterodorsal and the posteroventral VTA. However, the difference was not extreme, since neither the Nif nor Nln caudalis were reported to contain many labelled cells: the majority were in the other VTA nuclei.

In contrast to the topographical patterns of projection shown by neurons of the VTA (and SN), those from the raphe (5-HT) are less clear and from the LC (NA) almost absent (discussion[326]).

In conclusion mesocortical projections tend to have their origin dorsorostrally in the VTA (e.g. Nln rostralis not Npn). By contrast most mesolimbic projections originate in the ventrocaudal VTA (Npn and less from the midline)[352a,b].

2.2.14. *The efferent route.* A10 DA containing fibers consist of small diameter, non-myelinated axons[127] that ascend in the MFB medial to the crus cerebri (reviews[282,397]). The fibers are at first dorsolateral to NA containing fibers but ventromedial to those of the nigrostriatal pathway. Some crossing takes place caudal to the mammillary complex, although most fibers ascend ipsilaterally to the retrochiasmatic region. Some fibers deviate to the lateral habenula, and, at about the same juncture, those innervating the posterior forebrain follow the route of the amygdalofugal pathway and ansa lenticularis to the entorhinal, amygdaloid and piriform cortices.

The route of some of the fibers passing to the hypothalamus corresponds to the peduncularis mammillaris. Other fibers, after passing through the lateral hypothalamus, dorsal in the MFB, ascend past the rostral pole of the thalamus toward the septum. Before this dorsal flexure, components have branched off to the posterior hypothalamus, ventral striatum, accumbens, tuberculum olfactorium and dorsally to the diagonal band.

Whereas the amygdaloid and piriform components have descended in the external capsule, there are 4 other telencephalic components that continue to ascend. The prefrontal component (1) continues to ascend rostrally. Beneath these fibers, those (2) leading to the olfactory nuclei proceed rostrally from the first dorsal flexure. From the prefrontal component a branch (3) sweeps dorsally and caudally over the corpus callosum to the supragenual limbic cortex and another component (4) sweeps dorsocaudally be-

neath the callosum to the septum[9,32,127,229,230,364,412].

In primates fibers dorsal to the callosum pass rostrally to the frontal lobes following the contours of the gyri to the more distant regions. Fibers passing caudally join supracallosal stria and the cingulate bundle. Temporal and insular innervation courses ventrolaterally beneath the rostral stria[222].

Scatton[350] reported that about 70% of hippocampal DA is reduced by fimbria-fornix lesion. Thus it appears that most hippocampal DA fibers arrive by way of the dorsal route (including a few fibers in the cingulum), but that a minority may arrive by a ventral route over the amygdala and entorhinal cortex (amygdalofugal/angular bundle)[32,422]. There are no DA fibers in the perforant path.

There is some evidence that VTA efferents to the thalamus ascend in a separate bundle[367] that may be the equivalent of the so-called ventral periventricular system[230]. Fibers ascend on the internal edge of the lemniscus medialis to the ventral nuclei whilst a second bundle divides off to the more dorsomedial and dorsolateral nuclei.

Descending fibers spread dorsally then caudally over a wide area of the mesencephalic tegmentum. Most fibers continue in a caudal direction in the central gray, giving off a small branch to the cerebellum before passing over the LC[32,362]. In addition there is a small medial path projecting into the pons and a lateral path (rubrospinal tract) projecting to the olivary and facial nuclei[362].

2.3. *Afferent connections*

2.3.1. *Mes- and rhombencephalon.* The VTA receives a strong innervation from the dorsal raphe[57,82,317,364,396]. Further innervation from the 5-HT nuclei of the raphe magnus, pontis[317] and medianus[364,434] has been described.

Innervation has been reported from the catecholamine nuclei of the A1, A5, A6, A7 and A9[13,225,230,317,338,364,434] (i.e. the dorsal periventricular system, LC, ventral tegmental nucleus of Gudden, nuclei reticularis tegmenti pontis, caudalis and oralis and SN). Two cautionary points should be made. The dorsal and median raphe and the two tegmental nuclei of Gudden project to the N. interpeduncularis. Further the dorsal tegmental nucleus projects via the N. reticularis tegmenti pontinus to the VTA[225].

The N. dentatus and interpositus of the cerebellum project to the VTA[317,364,434]. Here another cautionary remark should be made. Phillipson[317] found that the cerebellar cells were particularly strongly labelled when injections to the VTA included part of the N. ruber. Further he noted that the cerebellar innervation of the A8 region was quite considerable.

The detailed study of the cat by Tork et al.[408] reported fibers innervating the VTA from areas lying close by in the tegmentum, posterior interpeduncularis and several raphe nuclei. From further afield there were VTA afferents from the LC and pontine tegmentum, vestibular, cuneate and gracile nuclei, spinal trigeminal and oculomotor nuclei, the deep cerebellum and ventral horn.

Most of these brainstem connections, with the exception of the extreme caudal examples, have been shown to be reciprocal in nature.

2.3.2. *Diencephalon.* A large part of the diencephalic input to the VTA is made up of fibers from the lateral habenula[3,170,317,364,384,408,434,438] and the lateral hypothalamus[43,118,153,184,317,433,434]. Phillipson also noted that the medial habenula not only sends fibers to the interpeduncularis but to the Nif as well[317] (cf. substance P[86,109]).

Projections are also received by the VTA from the lateral (and less so, the medial) preoptic nuclei, the anterior (and less so, the posterodorsal and ventromedial) hypothalamus[74,80,81,261,275,278,314,317,347,358,385,434]. Tork et al.[408] found fibers from all the hypothalamic nuclei, the medial and lateral mammillary nuclei of the cat. Retrograde transport was also found from the parafascicular nucleus of the thalamus[317].

There is some evidence that VTA afferent fibers from some areas may be crossed. Cerebellar, tegmental, superior collicular and red nucleus fibers were listed as examples in the cat[408].

A large proportion of fibers descend in the fasciculus retroflexus (Fig. 9).

2.3.3. *Telencephalon.* Many basal forebrain structures show reciprocal connections with the VTA, albeit in a reduced number and from slightly fewer sites; e.g. bed nucleus of the stria terminalis, diagonal band, substantia innominata, anterior, basal and central nuclei of the amygdala[80,118,155,180–182,195,261,298,317,328,385,408,409,434] and the accumbens[81,149,279,317,387,408,409]; cf. GABA fibers[426,434]. The claim for feedback from the tuberculum olfactorium has rarely been made[193,212,419]. A small input from the neostria-

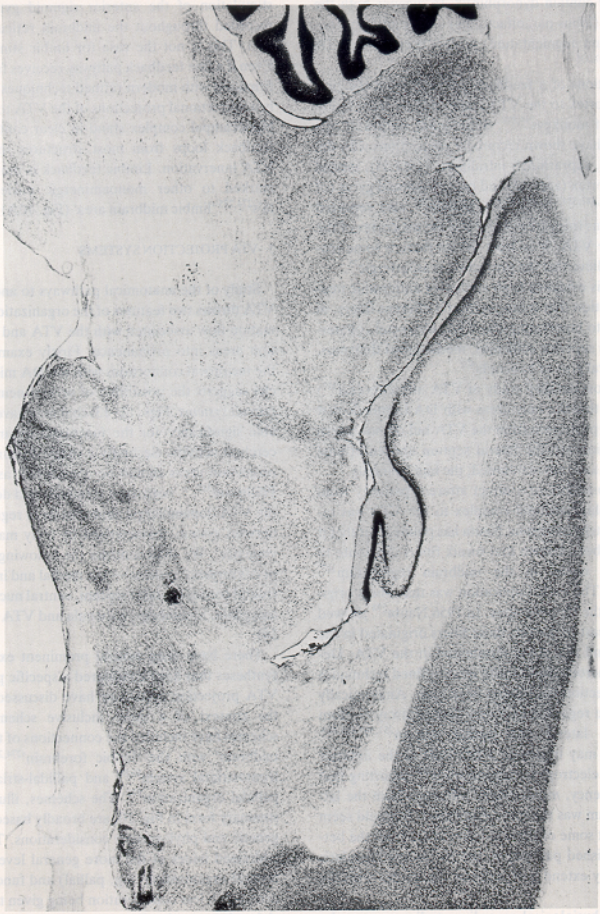

Fig. 9. Photomicrograph of rat brain in sagittal section (Nissl stain) showing the route of the fasciculus retroflexus in which descending afferent fibers pass to the VTA (Sutherland[384]).

tum may contain dynorphin[118]. In pigeons both the striatum (lobus paraolfactorius) and accumbens (paleostriatum augmentatum) project back to the VTA and SN[207,335].

Indications of a feedback pathway from the prefrontal cortex to the VTA came initially from lesion studies of monkeys[94,277]. Subsequent studies of rats and cats have shown reciprocal connections with the cingulate, suprarhinal, infralimbic (area 25), medial frontal cortex (area 32) and medial sigmoid gyrus (of cat)[31a,126,317,334,340,408,434,436]. Molina[267] also reported projections from areas 4 and 6 of the neocortex of the cat to the VTA. In at least the rat there is some reason to believe that the projection is aspartergic[75].

There is evidence from studies of antidromic neural activation that some prefrontal efferent fibers, in addition to innervating the VTA, also send collaterals to the superior colliculus, mediodorsal thalamus, SN, central gray or habenula[402].

The most detailed study of VTA afferents (rat[317]) reported that the only areas with DA terminals that receive a projection from the VTA but do not return a projection are the lateral septum and entorhinal cortex — and, not mentioned, the hippocampus.

The possibility of a direct afferent pathway from the septohippocampal complex to the VTA has received patchy attention. Nauta has pointed out that it has long been known that fornix fibers distribute to unknown nuclei in the midbrain tegmentum[107,137,139,210]. The early implication was that fibers originated in the hippocampus. In 1956 Nauta[274] showed that, at least in the rat, these fibers originated in the septum and that some terminated in the VTA. Despite numerous studies with more refined techniques this connection has seldom been seen. Anatomically it must be regarded as a very fine pathway — from both the lateral and medial septum[251,388,389,408,434] which may innervate a few cells in the anterior VTA (cf. electrophysiological study[248] reporting that a long-latency, *multisynaptic* influence from the lateral septum was the more dominant). It would seem likely that some of the confusion arises from the better established pathway to the N. interpeduncularis which may extend both sides of the border with the VTA[162].

Neurophysiological recording studies support the idea of a strong feedback from the neo- but not the allocortices. For example, afterdischarges that follow stimulation of the anterior sigmoid gyrus can be recorded throughout the midbrain reticular formation. This is not the case for limbic stimulation[147]. Even if a fine feedback pathway receives further confirmation with modern refined techniques, the largely unidirectional projections of the VTA to the septohippocampal complex stand in clear contrast to the feedback loops from most structures that receive VTA innervation. Limbic feedback is more strongly marked to other monoaminergic nuclei of Nauta's[274,275] 'limbic midbrain area' (Fig. 10A).

3. VTA PROJECTION SYSTEMS

Study of the anatomical pathways to and from the VTA throws two features of the organization of information flow associated with the VTA and its projection areas into prominence. Firstly examination of the reciprocal connections with the DA midbrain nuclei suggests the possibility of several neural circuits (*circuit systems*, Figs. 11–13) that may have considerable significance for the functional organization of cerebral activity. Secondly a major feature of VTA projection areas should be considered, as noted by Phillipson[317], '..both axon terminals and dendrites of the VTA dopaminergic neurones lie in regions of the nervous system characterised by truly massive convergence'. We shall consider the following examples of *convergence systems* — the medial and insular prefrontal cortices, lateral septum, central nucleus of the amygdala, accumbens, habenula and VTA (Figs. 14–16).

There have been several prominent examples of syntheses that have considered a specific part of the VTA projection system or have discussed it within the context of a more inclusive scheme. These schemes have included the connections of the 'limbic midbrain' with the 'limbic forebrain'[274,275,362], the frontostriatal system[96,98] and pallidal-striatal-nigropallidal organization[273]. The schemes, illustrated in summary form in Fig. 10, are broadly based on ontogenetic and phylogenetic considerations. They have addressed issues at the more general levels of anatomical organization (e.g. pallial) and function (e.g. drive) with less consideration being given to the special and contrasting features of connectivity (e.g. reduced limbic feedback, above), of function (e.g. post-VTA lesion syndrome[289a]) and the transmitters

and nuclei concerned (e.g. A9 vs A10). While it may be argued that these schemes can be related to some cognitive constructs arising from psychology, we suggest that a more realistic appraisal of the current understanding of the connectivity of the VTA projection system (sections 1 and 2) and its comparison with those arising from the A6, B7/8 and A9 nuclei can promote attempts to relate specific functions to a basis in the neurobiological circuitry. The following discussion is a first step in that direction.

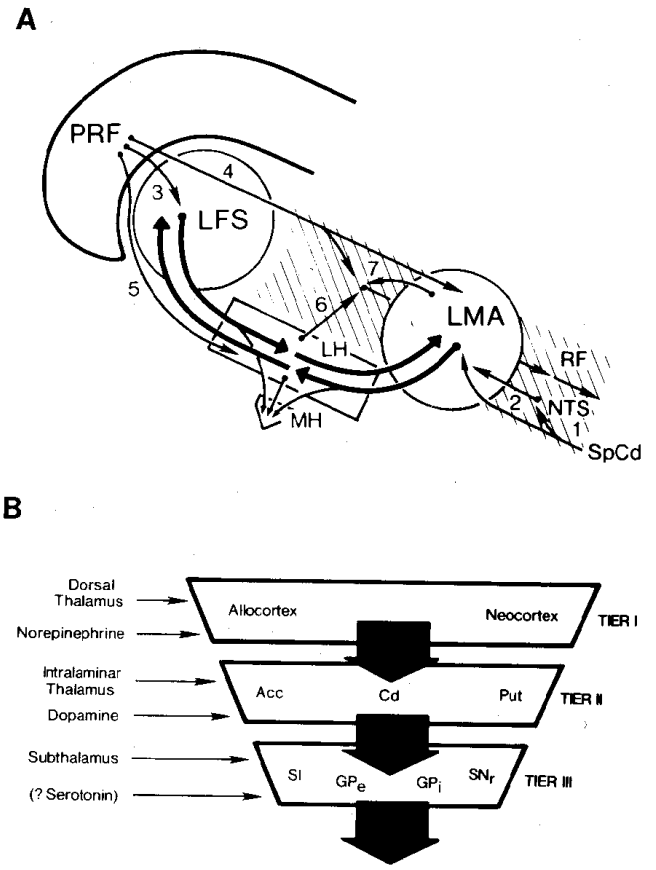

Fig. 10. A: schematic representation of the functional anatomical connections between the limbic midbrain area (LMA) and the limbic forebrain system (LFS) (after W. Nauta[275,276]; Simon[362]). Paths 1 and 2 ascend from the spinal cord (SpCd), relaying in part at the N. tractus solitarius (NTS). Paths 3, 4 and 5 are frontal (PRF) pathways projecting to the allocortical limbic system, lateral hypothalamus (LH) and reticular formation (RF). Paths 6 and 7 connect the hypothalamus (LH and MH) and LMA with the reticular formation. B: a schematic representation of the 3 tiers of organization proposed by H. Nauta[273] for the telencephalon and basal ganglia emphasizing common characteristics of internal histology, input–output patterns and characteristic neurotransmitters. The characteristic neurotransmitter and thalamic input is shown on the left. The arrows represent tier to tier output whereby every area of the first tier projects to part or parts of the next tier. Acc, N. accumbens; Cd, caudate nucleus; $GP_{e/i}$, external/internal pallidal segment; Put, putamen; SI, substantia innominata; SN_r, substantia nigra pars reticulata (non-dopaminergic).

3.1. *Circuit systems*

It has long been known that there is not only an ascending pathway from the SN to the striatum and frontal cortex, but also a descending reciprocal projection[99,106,166,209,264,304,336,425,432]. Thus it is surprising that the separate, yet somewhat parallel reciprocal innervation of the VTA was not recognized until 1958 (ref. 274).

The range of structures with which the whole ventral tegmentum is reciprocally connected suggests that it has a role in the control of function in the phylogenetically new and highly developed neocortex ('mesocortical system') as well as that of the phylogenetically much older limbic areas ('mesolimbic system').

Let us first consider the reciprocal connections with the polysensory association cortices. There is a widespread but quantitatively uneven innervation from the 5-HT and NA brainstem nuclei to these cortices. This innervation is denser than the patch-like distribution of DA cortical terminals, but the distribution of NA and 5-HT terminals is not so widespread as always to overlap with regions of DA inner-

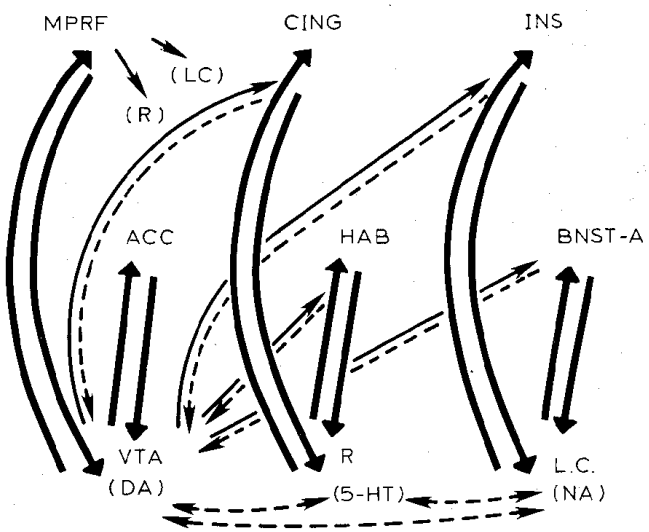

Fig. 11. Circuit system I: representation of the VTA innervation of those cortices that have major reciprocal connections with one of the main monoaminergic nuclei of the brainstem. Tentative parallels for 3 subcortical areas are also shown. In some instances the expression of regional contributions to behavioral organization involves communication between the monoaminergic nuclei at the level of the brainstem (e.g. HAB–R–VTA–MPRF) (for ref. see Fig. 15). MPRF, medial prefrontal cortex; CING, cingulate cortex; INS, insular cortex; ACC, N. accumbens; HAB, habenula; BNST-A, bed nucleus of the stria terminalis and amygdala; VTA, ventral tegmental area; R, raphe nuclei; LC, locus coeruleus.

vation. If we consider, from the point of view of potentially functional feedback circuitry, the limited reciprocal innervation that these nuclei receive, then one feature becomes prominent. Despite the discontinuous distribution of neocortical DA innervation, prominent VTA efferent terminals are found where other monoaminergic nuclei are also involved in a *marked* reciprocal dialogue (Fig. 11).

Thus, it may be possible to be selective and to separate the roles of the 3 'frontal' cortices (pre, supragenual and insular) on the basis of their dialogue with monoaminergic nuclei. More tentatively in Fig. 11 a similar scheme for 'subcortical' forebrain areas is suggested. This scheme selectively emphasizes a role for the unique reciprocal connections of these nuclei. It does not address questions of the functions of the range of structures found at different phylogenetic levels of organization. But it does attempt to point out interesting features of connectivity that may relate to the heterogeneity of function found at such levels.

Having attempted to contrast the ventral tegmental projection pattern with that of the other major monoaminergic nuclei, we now wish to contrast those from the SN and VTA within the ventral tegmentum. The VTA and SN have in common with each other a major dialogue with the frontostriatal system[95,98]. The emphasis of the SN is on the monosynaptic feedback from the neostriatum and that of the VTA on the mono- (and poly-) synaptic links with the association (neo- and allo-) cortices (Fig. 12). However, the

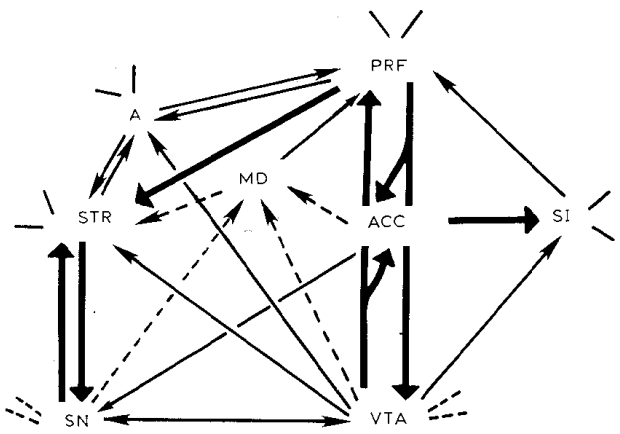

Fig. 12. Circuit system II: representation of the integration of ascending mesocortical with nigrostriatal DA systems. The diagram shows major (large arrows) and minor (small arrows) anatomical connections that provide alternative routes for input and feedback (for abbreviations see Figs. 11–13; for ref. see Fig. 15).

one projection system can affect the other (e.g. depletion of frontal DA with the toxin 6-OHDA is reported to induce an increase of DA receptor number in the neostriatum[145]).

Although many of the areas in Fig. 12 are interconnected we draw attention to the multiple nature of the routes by which DA systems originating primarily in the VTA can influence the function of the striatal complex directly or by way of modulating striatal afferent input. This is especially true if the SN is included in this term and the projection from the accumbens to the pallidum is also taken into consideration. (Further minor alternatives are suggested by the arrow roots, e.g. VTA to amygdala, substantia innominata etc.) The most important point is that the VTA can modulate activity at the cortical end of the frontostriatal system (cf. Divac et al.[96,98]).

Having discussed the interaction of midbrain systems with the neocortex (frontostriatal axis), now we wish to emphasize the limbic-striatal interactions (cf. allocortex, Fig. 10B). Here one observes the strong input to the accumbens from the allocortices and the VTA (Fig. 13). This parallels the neocortical and nigral input to the striatum. These parallel systems have considerable intrinsic interest[168,273]. But what about their interactions?

The accumbens occupies a crucial position in relaying descending information, especially that of allocortical origin. The output to the pallidum and SN

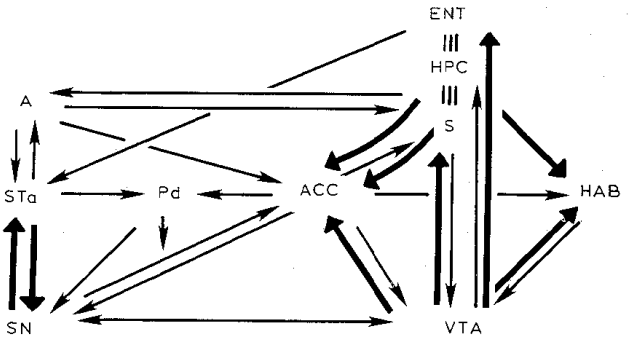

Fig. 13. Circuit system III: representation of the integration of ascending mesolimbic and nigrostriatal DA systems. The diagram shows the major ascending systems (large arrows), circuitry for interaction and the pallidal output pathway. A, amygdala; ACC, N. accumbens; ENT, entorhinal cortex; HAB, habenula; HPC, hippocampus; S, septum; STa, anterior neostriatum; SN, substantia nigra; VTA, ventral tegmental area. (Selected references and citations therein: VTA, SN, prefrontal cortex (PRF), insular cortex (INS)[32]; CC, SN[279]; LC, PRF, INS[73]; ACC[151,205]; ENT[377]; ACC, SN[382]; S, HAB[83]; LC, raphe nuclei (R), PRF[14,348,349]; A, mediodorsal thalamus (MD), CING, PRF[348,349]; INS[91].

shows firstly where much of the combined limbic/extrapyramidal communication occurs and secondly where the midbrain DA systems (in particular the VTA) can modulate this communication. (Note the W-like up and down connections between the two midbrain nuclei, the neostriatum and accumbens.)

The VTA DA system is in a position to play a crucial role in the limbic-basal ganglia dialogue. (Some would say it has a 'gating' role.) VTA activity not only modulates the input to the accumbens in the accumbens, but it may be transmitted directly to the septohippocampal complex, amygdala, prefrontal cortex to affect input to the accumbens at source and hence affect its output. The descending route passes over the accumbens to the neostriatum and pallidum to influence motor control. (Changes of striatal protein phosphorylation processes following impairment of hippocampal activity show that this route is functional[23].) The advantage of the route descending over the accumbens is that it allows for a broader influence for the limbic systems (fore- and midbrain) over the outcome of nigrostriatal activity.

An interesting feature that one might add is the cortical/subcortical interface provided by the septohippocampal complex[327]. The input/output components of the complex are closely associated respectively with the prefrontal-cingulate-insular level and the accumbens-habenula-bed nucleus-amygdala level (Fig. 13). From the point of view of future interpretations of function the septohippocampal complex should be viewed as being in receipt of monoaminergic afferents but its major or usual mode of feedback is indirect, by way of other subcortical regions.

A highly important feature of Figs. 12 and 13 is the presence of the substantia innominata and habenula to the right of each diagram (respectively). For, around these two structures and the accumbens in the middle of both figures revolves the interaction between mesolimbic and mesocortical circuits of the VTA DA system. Two nuclei of the thalamus that receive non-DA inputs may also be important for this side of mesolimbic/mesocortical interaction (N. medialis dorsalis and reuniens). The evidence derives not just from anatomical tracing techniques[151] but also the utilization of deoxyglucose after electrical stimulation[66]. Thus stimulation of the N. mediodorsalis activated the reuniens, accumbens, medial and sulcal prefrontal cortex. After N. reuniens stimulation the hypothalamus, amygdala, septohippocampal and prefrontal complexes were activated.

In all this we should not lose sight of the VTA itself in promoting dialoque between the mesolimbic and mesocortical systems. The VTA cells projecting to

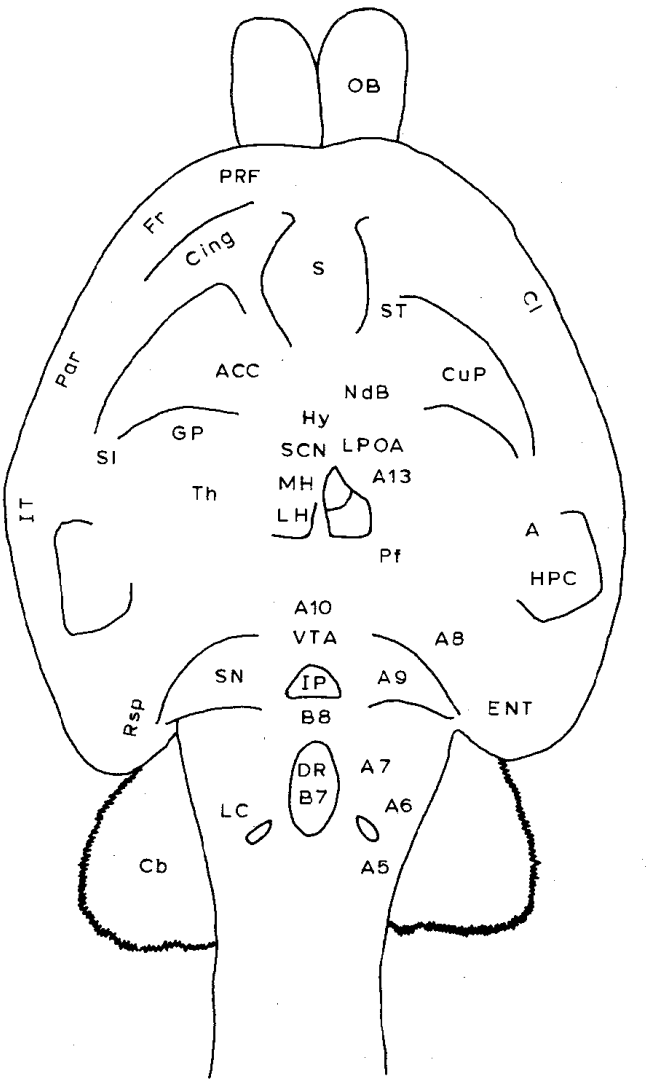

Fig. 14. Schematic plan view of the rat brain (rostral end at top of the diagram). Represented in bold print are the approximate positions of the nodal points of afferent convergence shown in Figs. 15 and 16: ACC, N. accumbens; ENT, entorhinal cortex; LH/MH, lateral and medial habenula; PRF, prefrontal cortex; S, septum; VTA, ventral tegmental area (A10). In fine print are the areas from which the afferents converge: A, amygdala; Cb, cerebellum; Cing, cingulate cortex; Cl, claustrum; CuP, caudate-putamen; DR, dorsal raphe (B7); Fr, frontal cortex; GP, globus pallidus; HPC, hippocampus; Hy, Hypothalamus; INS, insular cortex; IP, N. interpeduncularis; IT, inferotemporal cortex; LC, locus coeruleus (A6); LPOA, lateral preoptic area; NdB, N. of diagonal band of Broca; OB, olfactory bulb; PAR, parietal cortex; Pf, N. parafascicularis; Rsp, retrosplenial cortex; SCN, N. suprachiasmaticus; SN, substantia nigra (A9); ST, bed nucleus of the stria terminalis; Th, thalamus; Catecholamine (A1, A5–A10, A13) and 5-HT (B7, B8) nuclei.

the 'limbic' septum and habenula are those that receive prefrontal/cingulate input. Even within the mesolimbic system such a dialogue can be promoted: VTA cells receiving septal or preoptic input are those that project to the accumbens[386]. Thus one may list the structures important for the dialogue between A9 and A10 projection systems as the habenula, accumbens, substantia innominata, N. mediodorsalis, N. reuniens and the VTA.

The role of a 'circuit' is to facilitate dialogue and interaction. In this section we have attempted to show that the role of VTA DA systems is seminal, whether the circuits are viewed in terms of tiers of anatomically and embryologically related structures or as ascending mesotelencephalic projections based on transmitters of contrasting function.

3.2. *Convergence systems*

The notion of convergence systems arises from anatomical observations that there are some brain regions that receive an extraordinarily prolific and diverse input. The implication is that these areas are important for the assimilation of information or the association of diverse communications. They thus provide crucial areas for information processing and its modulation. That the more impressive examples all receive a DA innervation is a stimulus to the proposal that DA activity is responsible for increasing the probability of switches between sources of input competing for the control of the output of the convergence areas[287]. Classic examples are the lateral septum, central nucleus of the amygdala, the accumbens, lateral habenula, entorhinal and frontal cortex... and the VTA! (Fig. 14).

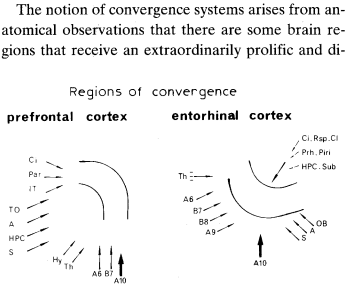

Fig. 15. Representations of the convergence of afferent input on mesocortical and mesolimbic DA projection regions. A, amygdala; Cb, cerebellum; Ci, cingulate cortex; Cl, claustrum; Ent, entorhinal cortex; Fr, frontal cortex; HPC, hippocampus; Hy, hypothalamus; IT, inferotemporal cortex; OB, olfactory bulbs; Par, parietal cortex; PrF, prefrontal cortex; Prh, perirhinal cortex; Rsp, retrosplenial cortex; S, septum; Th, thalamic nuclei; TO, tuberculum olfactorium; A, B 6–10, monoaminergic nuclei; VB, ventral noradrenergic bundle (Oades et al.[288]).

Firstly one may consider the septohippocampal complex. The allocortices receive input from a large array of sources that tend to converge in the lateral septum and entorhinal cortex[417] (Fig. 15). Both areas receive a DA innervation from the VTA. In both the coincidence of the convergence with DA input is so strong that one is inclined to think of the control and restriction of input, destined for the hippocampus, through a VTA DA gating mechanism[237a]. In the lateral septum and central nucleus of the amygdala neural elements are present that contain one (or more) of all the amino acids, monoamines and neuropeptides for which there is evidence of a neuromodulatory role in the CNS.

In the entorhinal cortex (Fig. 15) DA innervation is less extensive but occurs in clusters. It might be expected both to influence other specific inputs and to gate the propagation of information for propagation to the hippocampus[237a]. Control mechanisms may be particularly appropriate for the numerous and diverse sources of cortical input to the entorhinalis, that increase along the evolutionary series[31,77,117,216–218,231,270,376].

There is a massive input from the transition and allocortices to the accumbens (Fig. 15). But there is also some input from the related prefrontal regions. In contrast to the lateral septum, where there is a large diencephalic input largely from the hypothalamus, in the accumbens there is a multiple input from many thalamic nuclei. Interactions in the accumbens are capable of being modified by 5-HT, NA and DA from at least 5 separate brain areas[69,92,150,217,279,280,291,318a,425].

A detailed treatment of the frontal cortices (dorsolateral/medial prefrontal and sulcal) is beyond the

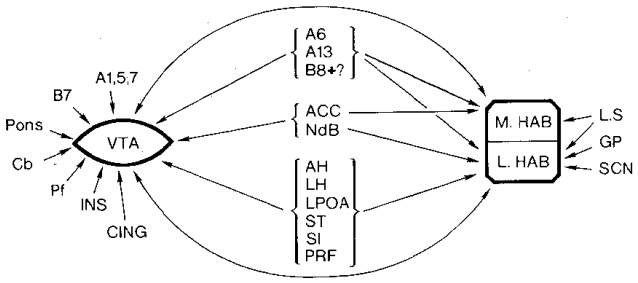

Fig. 16. Representation of the convergence of afferent input on the habenula and VTA. ACC, N. accumbens; AH, anterior hypothalamus; Cb, cerebellum; CING, cingulate cortex; GP, globus pallidus; INS, insular cortex; LH, lateral hypothalamus; L./M. HAB, lateral/medial habenula; LPOA, lateral preoptic area; L.S., lateral septum; NdB, nucleus of the diagonal band of Broca; Pf, N. parafascicularis; PRF, prefrontal cortex; SCN, suprachiasmatic nucleus; SI, substantia innominata; ST, bed nucleus of the stria terminalis; A1, A5–A7 (NA), A13 (DA), B7, B8 (5-HT), monoaminergic nuclei.

scope of this discussion. In summary this polysensory association cortex is in receipt of connections, in series and in parallel, from the other sensory association cortices (discussion[286]). Much of the indirect input passes over thalamic relays. There are trends in the evolutionary series for an increasing limbic innervation from the allocortices over and above the fundamental input from the hypothalamus. The information arriving in the prefrontal cortex can be modified successively in the different terminal zones by all 3 monoamines, GABA, acetylcholine and several neuropeptides (Fig. 15 (refs. 4, 12, 31a, 91, 116 and 253)).

The 'mesohabenular' system has, until recently, received relatively little attention (Fig. 16). Convergence at this nodal point is of special interest for the bringing together of input from both the basal ganglia and the limbic system. The habenula also provides via the stria medullaris an alternative route to the MFB for limbic-brainstem communication. The habenula complex, together with the VTA, raphe and pontine nuclei, may exert an important influence on the mesocortical and frontostriatal systems. The importance of this role may be deduced from the limbic representation amongst the habenula input. Further from a functional viewpoint what happens to the habenula affects transmitter activity in the frontal cortices (CAs and stress[235a]) basal ganglia and septo-VTA axis (intracranial self stimulation[136]). Interactions in the habenula are modulated by input from 3 monoamines, GABA and neuropeptides such as vasopressin and substance P[289,310,317,319,384].

Last but not least we should not omit the VTA itself from consideration as a nodal point (Fig. 16). We have already discussed the evidence for a broad range of input from each level of the brain from the neocortex to the brainstem. In addition there is evidence for interconnections with other DA neurons. Indeed probably 7 amines and at least 10 peptides have neuromodulatory roles in the VTA (Oades, in preparation).

Further research on the nature of the influence of the VTA, both within the neuronal circuit systems described in section 3.1. and on the nodal points of convergence described in section 3.2., will help to provide a basis for the explanation of the role of the VTA and its principal transmitter DA in modulating the processing of information and the organization of a wide variety of adaptive behavior. This understanding is essential for the development of improved approaches to treating the many clinical conditions that in part arise from dysfunction in VTA DA systems.

4. SUMMARY

The VTA contains the A10 group of DA containing neurons. These neurons have been grouped into nuclei to be found on the floor of the midbrain tegmentum — Npn, Nif, Npbp and Nln rostralis and caudalis. The VTA is traversed by many blood vessels and nerve fibers. Close to its poorly defined borders are found DA (A8, A9, A11) and 5-HT containing neurons (B8).

Efferent projections of the VTA can be divided into 5 subsystems. The mesorhombencephalic projects to other monoaminergic nuclei, the cerebellum and a fine projection descends to other tegmental nuclei as far as the inferior olive. Fibers to the spinal cord have not been demonstrated.

The mesodiencephalic path projects to several thalamic and hypothalamic nuclei and possibly the median eminence. Functionally important examples are the anterior hypothalamic-preoptic area, N. medialis dorsalis and reuniens thalami. These two subsystems are largely non-dopaminergic.

A minor mesostriatal projection is overshadowed by the large mesolimbic projection to the accumbens, tuberculum olfactorium, septum lateralis and n. interstitialis stria terminalis. There are also mesolimbic

connections with several amygdaloid nuclei (especially centralis and basolateralis), the olfactory nuclei and entorhinal cortex. A minor projection to the hippocampus has been detected.

The mesocortical pathway projects to sensory (e.g. visual), motor, limbic (e.g. retrosplenial) and polysensory association cortices (e.g. prefrontal). Prefrontal, orbitofrontal (insular) and cingulate cortices receive the most marked innervation from the VTA. A more widespread presence of DA in other cortices of rodents becomes progressively more evident in carnivores and primates.

Most but not all projections are unilateral. Some neurons project to more than one area in mesodiencephalic, limbic and cortical systems. The majority of these fibers ascend in the MFB. Most areas receiving a projection from the VTA (DA or non-DA) project back to the VTA. The septohippocampal complex in particular and the limbic system in general provide quantitatively much less feedback than other areas.

The role of the VTA as a mediator of dialogue with the frontostriatal and limbic/extrapyramidal system is discussed under the theme of circuit systems. The large convergence of afferents to certain VTA projection areas (prefrontal, entorhinal cortices, lateral septum, central amygdala, habenula and accumbens) is discussed under the theme of convergence systems.

Anatomical studies clearly demonstrate that the VTA in general and its DA projections in particular are strategically organized to influence integrative neural function in diverse regions of the mes-, di- and telencephalon.

ABBREVIATIONS

CNS	Central nervous system
DA	Dopamine
DOPAC	3,4-Dihydroxyphenylacetic acid
GABA	γ-Aminobutyric acid
HRP	Horseradish peroxidase
5-HT	Serotonin
HVA	Homovanillic acid
LC	Locus coeruleus
MFB	Medial forebrain bundle
N.	Nucleus
NA	Noradrenaline
Nif	Nucleus interfascicularis
Nln	Nucleus linearis
Npbp	Nucleus parabrachialis pigmentosus
Npn	Nucleus paranigralis
6-OHDA	6-Hydroxydopamine
PRF	Prefrontal cortex
SN	Substantia nigra
TOH	Tyrosine hydroxylase
VTA	Ventral tegmental area

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