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DOPAMINE (3-HYDROXYTYRAMINE) AND BRAIN FUNCTION

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I. INTRODUCTION

In addition to norepinephrine and epinephrine, there occurs in vertebrates and invertebrates a third catecholamine; this is dopamine (3-hydroxytyramine; β-3, 4-dihydroxyphenylethylamine). It is now well established that dopamine is the immediate precursor in the formation of norepinephrine in chromaffin tissue and noradrenergic nerves (see figure 1, below). The pharmacological activity of dopamine has been known for a long time (21, 132). In most, but not all, test preparations its peripheral actions are qualitatively like those of norepinephrine and epinephrine, and one is therefore justified in classifying it as a sympathomimetic amine. It was not until 1957 that the suggestion was made that, apart from its role as the immediate precursor of norepinephrine in the body, dopamine might have a physiological function of its own (46). At the same time, the possibility of central actions of dopamine was envisaged (62).

Great difficulties are encountered in the study of physiologically occurring substances in brain function. Many criteria have to be satisfied (see 99) before any substance can be regarded as acting on the nervous system in a physiological way. It will be understood that it is not an easy task to show this for an organ like the brain, with about 10^{10} nerve cells, most of them being functionally dependent on, or connected to, each other. "Enthusiasm for chemical transmission has not always been combined with critical assessment of the results being offered and there has been a tendency to lose sight of the essential quality of a transmitter

substance." This statement, made by Crossland (70), describes very clearly the present situation in the field of chemical transmission in the central nervous system. Despite all these difficulties the writer believes that there is strong evidence that dopamine may be important in brain function. The aim of this article is to present the pertinent evidence for this view.

In recent years, special aspects of dopamine's effects on the central nervous system have been reviewed by several authors (35, 94, 137, 139, 219, 220).

II. GENERAL ASPECTS

A. Dopamine as precursor of other compounds

1. Brain norepinephrine. The role of dopamine as the immediate precursor in the biosynthesis of norepinephrine is well established (for reviews see 47, 206). Norepinephrine occurs in the brains of many mammalian and submammalian species (41, 52, 57, 87, 129, 192, 241), and there is good reason to assume that the amine is being synthesized in the brain at the sites of its occurrence. Since there is evidence that norepinephrine plays a physiological role in the functioning of certain neuronal systems in the brain (98, 242), the importance of dopamine metabolism for noradrenergic structures in certain brain regions is obvious. From this it follows that changes of dopamine metabolism in these regions (*e.g.*, disturbances of synthesis or storage mechanisms) are bound to affect, in an indirect way, the functioning of the assumed noradrenergic structures.

2. Brain melanin. The occurrence of melanin-containing nerve cells in some areas of the brain has been a puzzle ever since its discovery. In this respect, the melanin-containing neurons of the substantia nigra deserve special consideration.

Substantia nigra is relatively rich in catecholamines and 5-hydroxytryptamine, dopamine being the predominant catecholamine in this area (for details see Section III A). There is good reason to assume that dopamine is concentrated in those nigral nerve cells that also contain melanin. The possibility thus exists that the nigral melanin might be derived either from dopamine itself or from its precursor L-dihydroxyphenylalanine (L-dopa). The fact that differences have been found to exist between melanin from the skin and neuromelanin (the former is thought to be dopa-melanin) (159), favors the assumption that nigral melanin may be formed from compounds other than dopa. The recent findings by Vanderwende (238) seem to support this assumption. The author presented evidence that rat brain homogenates could oxidize dopamine, but not dopa or norepinephrine, to a black pigment, which possessed the properties of dopamine-melanin. The author did not identify the enzyme system responsible for this reaction, but he thought that participation of enzymes like the cytochrome system or monoamine oxidase could be excluded. The idea suggests itself that neuromelanin may be a by-product of the biosynthesis of catecholamines.

The above arguments are by no means invalidated by the fact that the caudate nucleus and putamen (these constitute the corpus striatum or striatum), which contain most of the brain dopamine (see Section III A), are usually devoid of melanin. As evidence has been presented (see Section III B) that dopamine in the striatum is localized in nerve terminals, it may be presumed that the ability

to form melanin from dopamine is confined solely to the nerve cell bodies, the axons and terminals being devoid of the necessary enzyme systems.

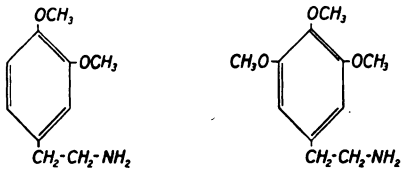
Recently, it has been proposed (163) that neuromelanin might be concerned with the regulation of the rate of catecholamine synthesis in the pigmented brainstem nuclei. This hypothesis is based on the observation that in the melanin granule the center contains enzymes, including tyrosinase, the melanin "shell" being a barrier to the access of enzyme to substrate. It is assumed that melanin formation would therefore diminish tyrosinase activity and catecholamine synthesis in certain brain cells. This stimulating hypothesis does not account for two facts: (a) that "over-production" of catecholamines could be efficiently disposed of by other biochemical mechanisms, such as inactivation by monoamine oxidase or catechol-O-methyltransferase, or binding in inactive form, and (b) that there is no evidence that the melanin-forming enzyme "tyrosinase" is identical with the tyrosine hydroxylase; only the latter enzyme is concerned with catecholamine synthesis.

3. Methoxyderivatives of dopamine. In 1932, Epstein *et al.* (83) examined the physiological actions of a series of methoxyphenylethylamines related to epinephrine. They observed that in cats 4-methoxy-, 3-methoxy- and methylene-3,4-dioxyphenylethylamine caused tremor, ataxia, and finally convulsions, while the animals that received 3,4-dimethoxyphenylethylamine became gradually paralyzed.

Recently these studies were resumed (84) after it became known that O-methylated catecholamine derivatives might accumulate in the body through the action of the enzyme catechol-O-methyltransferase (13). It was found that administration of 4-methoxy and 3,4-dimethoxyphenylethylamine to cats provoked a striking "hypokinetic rigid syndrome" (84). The presence of an OCH_3 group on the *para* position in the phenol ring was essential to produce the "hypokinetic rigid syndrome"; introduction of a second OCH_3 group adjacent to the one in the *para* position prolonged the syndrome (85). In contrast, occupation of the *meta* position by an OH or OCH_3 group in the absence of similar groups at the *para* position caused hyperkinesia in rats (86). On the basis of these findings, the suggestion was made that in human patients phenomena of the hypokinetic rigid type might be caused by O-methylation of brain dopamine in the *para* position (84).

The akinetic action of 3,4-dimethoxyphenylethlamine has been confirmed in mice, rats, rabbits and monkeys (20). Moreover, the compound was found to occur in high concentrations in the urine of patients suffering from Parkinson's disease (16). From these findings and those reported above, the interesting working hypothesis has been proposed that akinesia in parkinsonism may be caused by an error of dopamine metabolism of the extrapyramidal centers of the brain (see Section III A and V A) leading to formation of its 3,4-dimethoxyderivative (20).

Another research group reported on the isolation of 3,4-dimethoxyphenylethylamine from the urine of schizophrenic patients (101, 102), and conversion of exogenous dopamine to 3,4-dimethoxyphenylacetic acid in schizophrenic patients



3.4-dimethoxyphenylethylamine — I

3.4.5-trimethoxyphenylethylamine = mescaline — II

(103). These findings have been confirmed by several investigators (153, 213, 232), but two negative reports have also been published (97, 186). The connection between 3,4-dimethoxyphenylethylamine and schizophrenia would open interesting possibilities for future research because of the chemical similarity of this compound to mescaline, the 3,4,5-trimethoxy-analogue of dopamine (see chemical formulas I and II). The latter compound has for a long time been known to produce abnormal mental states, often called "experimental psychoses." It is interesting to note that as early as 1952 it was suggested that a number of amines structurally related to mescaline, including 3,4-dimethoxyphenylethylamine, should be investigated as to their psychotogenic effect. (183).

Since high amounts of 3,4-dimethoxyphenylethylamine seem to occur in the urine of both parkinsonian and schizophrenic patients, too much importance should not be attached at present to this finding. More direct evidence, *e.g.*, occurrence in brain of parkinsonian or schizophrenic patients, or both, must be awaited before a conclusion can be reached on this aspect of dopamine metabolism.

B. Dopamine as a physiologically active substance in its own right

It seems that Blaschko (46) was the first to consider the possibility that dopamine might have a dual role in the periphery: that of a precursor in the biosynthesis pathway of norepinephrine and epinephrine, and, in addition to this, a physiological role of its own. In the past few years, a considerable body of evidence has been accumulated that in the periphery as well as in the brain dopamine may possess physiological functions different from those of norepinephrine.

1. Periphery. A detailed account on the possible physiological significance of dopamine in the periphery is outside the scope of this review, but a brief discussion of this aspect is justified, so as to show that some of the peripheral actions of dopamine do possess features which clearly distinguish this amine from norepinephrine.

As a rule, dopamine is a comparatively weak sympathomimetic agent in the periphery (21, 132). The fact that it has such actions shows that it can combine with the classical sympathomimetic receptors (see 12). In a study on different types of sympathomimetic α-receptors, van Rossum (196) showed that the α-receptors in the vas deferens of the rat have a considerably higher affinity for dopamine than the α-receptors in the rabbit intestine. Although these observations do

not prove the existence of special dopamine receptors in peripheral tissues, it is interesting to note that, in respect to their affinity for dopamine, large quantitative differences between different α-receptors may be found.

In 1942, Holtz and Credner (131) made the important observation that dopamine could exert an effect qualitatively different from that of norepinephrine. The authors found that in the guinea pig and, to a lesser extent, in the rabbit, dopamine, in contrast to norepinephrine, caused a fall in the arterial blood pressure. This finding has been confirmed by many authors (55, 78, 136, 204). The vasodepressor action of dopamine in the guinea pig seems to represent an activity intrinsic in the amine; it is not due to compounds produced when dopamine is oxidized by monoamine oxidase (136; about metabolites of dopamine with depressor activity, see 133). In recent studies it has been shown that also in other species dopamine has actions on the vascular system different from those of norepinephrine. Unlike norepinephrine, it increases the blood flow through the superior mesenteric vessels and celiac vessels in the dog (80) and through the kidney in the dog and in man (80, 166, 167, 178; see also 2). It must be stressed that all these specific actions of dopamine in different species are not affected by α- or β-blocking agents (80, 133, 166, 178, 240).

These observations strongly suggest the possibility that in the periphery there exist specific dopamine receptors which differ qualitatively from the hitherto known sympathomimetic α- and β-receptors.

To support the role of dopamine in the periphery one can refer to the reports by different investigators on the occurrence of the amine in peripheral tissues, such as adrenergic nerves and ganglia (90, 156, 204), blood vessels (91), heart (11, 36, 114), lung, bronchi (90), liver and intestine (205). In many of these organs dopamine accounts for as much as 50 per cent of the total catecholamine content. In some (lung, bronchi, liver, intestine) it is the only catecholamine detectable. The small amounts of dopamine in the adrenal medulla [about 2 per cent of the total catecholamine content (78, 114, 216)] represent, most probably, only an intermediate stage in the biosynthesis of norepinephrine and epinephrine. There is some evidence to show that in the lung, liver and intestine of ruminants dopamine resides in a special type of chromaffin cell (36) which is believed to belong to the mast cell group (1, 95). No such cells have been found in species other than ruminants (57).

Since dopamine has its peculiar peripheral actions and occurs in different tissues it might in fact possess physiological functions of its own in the periphery, independent of, and different from, those of norepinephrine. However, since no direct evidence has so far been presented that there might exist in the periphery true dopaminergic neurons, at present no transmitter function for peripheral dopamine can be postulated.

2. Brain. Direct and indirect evidence indicates that brain dopamine satisfies many criteria of a physiologically active substance. Findings pertinent to this question will be discussed at length in the following sections. In the context of this section it seems profitable to mention briefly those arguments which are best suited to point out the differences between dopamine and norepinephrine in the

brain. These findings are: (a) In the brain ganglia of molluscs, dopamine is the only detectable catecholamine. Electrophysiological evidence shows that in this phylum dopamine has actions on nerve cell activity different from those of norepinephrine and epinephrine. (b) In mammals the highest concentrations of dopamine are found in some brain regions (especially those belonging to the extrapyramidal motor system, *e.g.*, striatum, globus pallidus, substantia nigra) which contain only small amounts of norepinephrine, and there is nothing to suggest that these low concentrations of norepinephrine could be due to a particularly high turnover of this amine. (c) Recent observations show that there are dopamine-containing neurons originating in the substantia nigra and running, in all probability, to the striatum, and that degeneration of the substantia nigra makes the dopamine in the striatum disappear.

The above arguments do not, by themselves, allow any definite conclusions as to the specific physiological role of dopamine in the brain. They do show, however, that there are good reasons to assume that such a role may in fact exist.

III. PHYSIOLOGICAL SIGNIFICANCE OF BRAIN DOPAMINE

A. Occurrence and regional distribution

1. Lower animals (invertebrates and lower vertebrates). In *Crustacea* (extracts of the shrimp, *Crangon cragon*) Östlund (184) was unable to find any chromatographic evidence for the presence of the amine.

In insects, the occurrence of dopamine is well documented. As early as 1938, Wense (248) found a catechol compound in extracts of mealworms. Östlund (184) presented convincing evidence for the occurrence of dopamine in various insects, its concentration being 10 to 20 times that of norepinephrine. Recent findings, however, indicate (212) that in insects dopamine is probably only an intermediate in the formation of N-acetyldopamine. The latter compound has been shown to be involved in the tanning process, representing the actual sclerotizing agent of the cuticle both of the puparium and of the imago. No observations seem to have been made on the possible occurrence of dopamine in the nervous system of insects.

In molluscs, although Östlund (184) was unable to find any conclusive evidence for the presence of dopamine, the occurrence of this amine in the nervous tissue of many members of this phylum now seems to be firmly established. Using paper chromatographic, colorimetric, and spectrofluorimetric methods, many research groups have detected microgram quantities of dopamine per gram of tissue in the cerebral and visceral ganglia of a great variety of molluscan species (56, 75, 146, 228). Moreover, the nervous tissue of *Helix pomatia* was shown to convert dopa to dopamine *in vitro* (56). In a study of a number of lamellibranch and gastropod species Sweeney has found as much as 261 μg of dopamine per gram of nervous tissue of *Mercenaria mercenaria*; he found no epinephrine or norepinephrine there (228). The latter finding is consistent with the reported absence of these amines in *Mytilus* (89). In *Mercenaria*, dopamine seemed to be concen-

trated exclusively in the ganglia, with other tissues such as gill, mantle and heart containing no detectable concentrations of the amine (228).

In the pigeon, dopamine is concentrated in those parts of the telencephalon commonly referred to as "striatum" (33, 37). A more detailed study of the striatum complex in this species revealed that the highest concentrations of the amine, and its metabolite homovanillic acid, are in the anterior part of the nucleus basalis (144).

2. Mammals, including man. a. Dopamine. As the occurrence of norepinephrine in the mammalian brain has been known for a long time (see Section II A), the presence of small amounts of dopamine, its immediate precursor, in the brain was to be expected. Montagu (180) and Weil-Malherbe and Bone (245) were the first to present evidence that dopamine is a normal constituent of the mammalian brain. Since then, dopamine has been found in the brain of all mammalian species examined (34, 39, 41, 57, 63, 81, 156, 188, 201, 205, 249, and many others). The finding that in most species the amine accounted for as much as 50 per cent of the total catecholamine content of the whole brain (63, 205) does not support the opinion that dopamine is exclusively a precursor of brain norepinephrine.

In 1959, Bertler and Rosengren as well as Carlsson (39, 57) reported on a decisive study showing that the *regional distributions* of dopamine and norepinephrine in the mammalian brain were markedly different. Little dopamine was found to occur in the norepinephrine-rich hypothalamus, the highest amounts of dopamine being present in the caudate nucleus and putamen (the striatum) regions belonging to the so-called extrapyramidal motor system of the brain. This important observation has since been confirmed by numerous authors (81, 156, 188, 201), and extended to the substantia nigra (34, 81, 138, 201) and the globus pallidus (34, 81, 201) (see table 1). In view of these findings, it may be relevant that, as early as 1951, Raab and Gigee (192a) found a catecholamine-like compound in particularly high amounts in the caudate nucleus of animals (monkey, dog, pig, ox) and of man.

The difference in the local distribution of norepinephrine and dopamine is best illustrated by comparing the corresponding figures for different brain regions. Thus, in the caudate nucleus, which is nearly devoid of norepinephrine (0.1 μg/g or less), the concentration of dopamine is on the average 10 μg/g of fresh tissue. In contrast, the dopamine concentration in the norepinephrine-rich hypothalamus rarely exceeds 10 per cent of the concentration of norepinephrine, the latter ranging between 1 and 2 μg/g in this region. In the substantia nigra and the pallidum dopamine is the predominant catecholamine, its concentration in these regions exceeding that of norepinephrine roughly by a factor of 10 (27, 34, 138). There are findings to suggest that dopamine may be the predominant catecholamine also in the retina (118, 119), the tuberculum olfactorium (4) and the infundibulum (117). Recently Laverty and Sharman (156) have found high amounts of dopamine in the median eminence and pituitary stalk of the cat, sheep and goat (see table 1). Reports on the occurrence of dopamine in the spinal

TABLE 1

Regional distribution of dopamine (μg/g wet tissue) in the brain of some mammalian species

Brain Region	Man	Monkey *f*	Pig *g*	Dog	Cat	Sheep	Goat	Rat	Rabbit
Cerebral cortex	0.13 *a*	—	—	0.01 *h*	0.07 *h*	—	—	0.01 *h*	—
Hippocampus	0.04 *a*	—	0.04	0.13 *g*	0.08 *g*	0.06 *g*	—	—	—
Caudate nucleus	5.74 *a* 3.5 *b* 3.12 *c*	3.12	6.1	5.90 *g* 9.9 *h*	8.00 *g* 9.9 *h*	6.68 *g* 11.78 *h*	10.9 *h*	6.39 *h*	7.38 *i*
Putamen	8.25 *a* 3.7 *b* 5.27 *c*	3.66	—	—	—	—	—	—	—
Lentiform nucleus	—	—	3.6	1.63 *g*	1.90 *g* 8.22 *h*	4.78 *g*	—	—	—
Pallidum	0.5 *b*; 0.32 *c*	—	—	—	—	—	—	—	—
Pars externa	0.19 *d*								
Pars interna	0.04 *d*								
Thalamus	0.46 *a** 0.03 *c*	—	—	0.05 *h***	0.05 *h***	0.34 *h***	0.31 *h***	—	0.10 *h* *
Hypothalamus	1.12 *a* 0.22 *c*	—	0.88	0.26 *g* 0.25 *h*	0.75 *g* 0.20 *h*	0.19 *g* 0.27 *h*†	0.15 *h*†	0.14 *h*	0.20 *h*
Median eminence + pituitary stalk					1.3 *h* 1.8 *h*	5.05 *h*	2.0 *h*		
Mesencephalon			0.14	0.20 *g* 0.33 *h*	0.19 *g* 0.15 *h*	0.24 *g*	0.41 *h*‡	0.13 *b*	0.18 *h*
Substantia nigra	0.38 *b* 0.46 *e*	—	—	—	—	—	—	—	—
Pars compacta	0.76 *e*								
Pars reticularis	0.34 *e*								
Pons	0.07 *a*	—	0.06	0.10 *g*	0.11 *g*	0.04 *g*	—	—	—
Medulla	0.17 *a*	—	0.05	0.13 *g*	0.08 *g*	0.17 *g*	—	—	—
Cerebellum	0.00 *a* 0.02 *c*	—	0.01	0.03 *g*	0.02 *g*	0.03 *g*	—	—	—
Retina	—	—	—	—	—	—	—	—	5.3 *j*

The figures are taken from: *a*, from (201); *b*, from (81); *c*, from (34); *d*, from (141); *e*, from (138); *f*, calculated from (188 and 222); *g*, from (41); *h*, from (156); *i*, calculated from (211); *j*, from (119).

*, medial nuclei; **, massa intermedia; †, superior hypothalamus; ‡, anterior midbrain.

cord are controversial at present. McGeer and McGeer (170) found it to be the main catecholamine in the spinal cord of the rat, rabbit, ox, cat, hog and man. Other authors, however, were unable to find substantial amounts of this amine in the spinal cord (3, 156, 160).

As will be discussed below in detail (see this Section, D) there is no reason to assume that differences in turnover rates of dopamine and norepinephrine could

possibly account for the high amounts of dopamine found in regions containing only little norepinephrine. This can be concluded from the findings that the turnover rate of dopamine in these regions is equal to, or even higher than, that of norepinephrine.

b. Homovanillic acid. As is to be expected, the distribution of homovanillic acid, the main metabolic break-down product of dopamine in brain (see this Section, D, and fig. 1) roughly parallels the distribution of the amine (24, 214). However, quantitative differencies seem to exist which are worth mentioning (24, 31). Whereas in the striatum the ratio of dopamine to homovanillic acid varies, according to species, between 4 (cat) and 0.5 (dog) (157), the corresponding figures for the substantia nigra and the pallidum (man) are 0.25 and 0.04 respectively (31). This finding suggests that, in spite of the low actual concentration of dopamine in the substantia nigra and the pallidum, the amine in these regions might be present in physiologically active concentrations comparable to those found in the striatum. (The significance of this finding is further discussed in this Section, B 3).

B. Cellular localization

The information concerning the cellular localization of dopamine in the brain comes almost exclusively from fluorescence microscopic evidence published by several Swedish research groups. The method used throughout these studies was recently described in detail by Falck and Owman (96). It should be kept in mind that with this method it is at present impossible to distinguish between the fluorescent compounds formed from dopamine and those formed from norepinephrine. To overcome this difficulty, most investigators performed control studies with drugs which are known to influence the metabolisms of dopamine and norepinephrine *in vivo* to different degrees. Since the specificity of any drugs used is limited, the writer feels that the most reliable observations of this kind are those which combine fluorescence microscopy with one of the more direct methods for estimation of catecholamines in biological material, *e.g.*, spectrofluorimetry of purified tissue extracts. This restriction, however, should by no means invalidate the most valuable information obtained by the fluorescence microscopic method.

1. Dopamine-containing nerve cells. Evidence has been presented that the dopamine occurring in the ganglia of molluscs, is concentrated in nerve cells which give rise to dopamine-containing nerve fibers (75).

In the *mammalian brain*, fluorescence due to dopamine-containing nerve cells was mainly found in the pars compacta of the substantia nigra (76). The fluorescence microscopic observation is in accord with the biochemical finding that most of the dopamine present in the substantia nigra of man (34, 81, 201) occurs in the pars compacta of this region (138). In the dopamine-rich striatum, either only faintly fluorescent nerve cells (58) or no fluorescent nerve cells (105) have been detected. From studies in human brain, the opinion had been expressed (81) that in the striatum dopamine is contained neither in the glial cells nor in the small multipolar neurons which account for about 95 per cent of the striatal nerve cells. In that study the possibility could not be excluded that dopamine

was contained in the larger striatal neurons; the negative fluorescence microscopic evidence seems to deny this possibility.

In agreement with biochemical findings, dopamine-containing nerve cells have been observed in the retina (rat, rabbit) between the inner plexiform and the inner nuclear layer (119, 161). There is also some evidence that the nerve cells in the arcuate nucleus and the ventral portion of the anterior periventricular nucleus of the hypothalamus, which display the typical catecholamine fluorescence and which give rise to nerve terminals running to the primary capillary plexus of the hypophyseal portal system (see below), are of the dopamine type (76, 104). The occurrence of dopamine-containing cell groups in the lower brain stem has been considered (76), but there is at present no biochemical evidence for this possibility. No fluorescent material has been observed in glial cells.

2. Dopamine-containing nerve terminals. Although, owing to the diffuse fluorescence of the whole area, no dopamine-containing fibers could originally be observed in the corpus striatum (58), the presence of dopamine-containing terminals in this region is now generally accepted. It seems that these fibers are unusually fine (some of them invisible with the light microscope) and so closely packed that individual terminals are extremely difficult to observe by means of the fluorescence microscope (107). The presence of dopamine-containing terminals has also been assumed in the nucleus accumbens (which belongs anatomically to the striatal complex), the tuberculum olfactorium, and the median eminence (106). Some dopamine terminals have also been assumed to be present in certain nuclei of the low brain stem and in the hypothalamus (for details, see 106). In the pars compacta of the substantia nigra a few nerve terminals containing a catecholamine (probably norepinephrine) have been detected (106). Varicose nerve terminals associated with the capillaries of the primary plexus of the hypophyseal portal system have been observed in different species. They are thought to contain mainly dopamine and to originate from the arcuate nucleus and the periventricular nucleus of the hypothalamus (104).

3. Dopamine-containing nerve fibers. Since the dopamine content of the fibers of dopamine-containing nerve cells seems to be very low under normal conditions, it is not easy to make them visible in the fluorescence microscope. Despite these difficulties, dopamine-containing fibers have been observed in the ganglia of molluscs (75), in the retina of the rat and rabbit (119, 161) and within the basal ganglia complex of the rat brain. With regard to the latter localization, it now seems to be accepted that most, if not all, of the dopamine fibers of the basal ganglia complex belong to the pathway connecting the substantia nigra with the striatum (76, 140, 188).

The existence of dopamine-containing nigro-striatal fibers is strongly supported by studies of the effect of making lesions in certain areas of the mid- and forebrain on dopamine in the brain. In human parkinsonism there exists a close relationship between the degeneration of the substantia nigra and the low dopamine content of the striatum (81, 138, 139). Lesions placed within the midbrain or the pallidum (including the internal capsule) in experimental animals (monkey, rabbit, rat) also cause the dopamine content of the striatum to fall;

TABLE 2

Dopamine and homovanillic acid (μg/g wet tissue) in some extrapyramidal centers of normal human subjects and patients with idiopathic Parkinson's disease and postencephalitic parkinsonism

Brain Region	Normal		Parkinson's Disease		Postencephalitic Parkinsonism	
	Dopamine	Homovanillic acid	Dopamine	Homovanillic acid	Dopamine	Homovanillic acid
Caudate nucleus	2.46 *a*	3.38 *a*	1.1 *e* 0.42 *f*	1.19 *f*	0.2 *e* 0.05 *f*	0.49 *f*
Putamen	3.43 *a*	3.47 *a*	0.8 *e* 0.01 *f*	1.05 *f*	0.3 *e* 0.04 *f*	0.58 *f*
Pallidum	0.30 *b*	2.4 *c*	—	0.58 *f*	0.1 *e*	0.32 *f*
Substantia nigra	0.46 *d*	1.8 *c*	—	—	0.07 *a**	0.41 *a**

The figures are taken from: *a*, from (31); *b*, from (139); *c*, from (24); *d*, from (138); *e*, from (81); *f*, from (28).

*, In these cases no differentiation was made between idiopathic Parkinson's disease and postencephalitic parkinsonism.

this has been shown by both biochemical and fluorescence microscopic methods (5, 37, 188, 211). It can be assumed that in all these instances a dopamine-containing pathway connecting the substantia nigra with the striatum has been interrupted, the lowered dopamine content of the striatum being due to degeneration of the corresponding terminals. Problems concerning the exact course of the nigro-striatal fibers and some of their neurochemical and morphological features are discussed in Section V B.

It is worth noting in this connection that although the existence of nigro-pallidal fiber connections is generally assumed (see 69), no dopamine-containing terminals have been detected in the pallidum. This is the more surprising as neurochemical work in human brain clearly showed that distinct, though low, amounts of dopamine are found especially in the pars externa of this nucleus (141), and that the concentration of homovanillic acid in the whole of globus pallidus is rather high (24) (see table 2) indicating a rapid turnover of the pallidal dopamine. Since the neurochemical work in question does not allow any conclusions concerning the cellular localization of dopamine, the possibility must be kept in mind that at least part of the amine might also be localized in the nigro-striatal fibers coursing through the pallidum. This assumption would help to explain the finding that after coagulation of the pallidum, including the internal capsule, the dopamine concentration of the caudate nucleus of the rabbit fell considerably (211).

Since most, if not all, of the striatal dopamine is concentrated in nerve terminals that are assumed to originate in the substantia nigra, the conclusion seems inevitable that the number of these terminals is very large, as judged from the

diffuse and very strong characteristic fluorescence observed in the striatum. This is puzzling in view of the fact that the size of the pars compacta of the substantia nigra is only a fraction of that of the whole striatum.

C. Subcellular distribution

The available evidence concerning the subcellular distribution of brain dopamine is scanty. In early experiments, in which homogenates of rabbit brain stem were used, dopamine was found to be equally distributed between the particulate and the supernatant cell-fractions (245, 246). Recent studies with caudate nuclei from cats and dogs and whole brains of rabbits indicated that the percentage of particle-bound dopamine may be even smaller than orginally found (20 to 30 per cent of total amine), the bulk of the amine being recovered in the "cytoplasmatic sap" (38, 247). Recently, the distribution of dopamine in subcellular fractions from homogenates of the dog caudate nucleus was compared with the distributions of acetylcholine, 5-hydroxytryptamine, and lactate dehydrogenase activity (155). The results of this study compared favorably with those of previous studies. In contrast to acetylcholine, most of the dopamine was recovered in the soluble supernatant fraction, and the remainder was associated with fractions rich in "pinched-off" nerve ending particles. In view of these findings, the authors even considered the possibility that the dopamine in the caudate nucleus may occur in a free or easily released form throughout the cytoplasm.

It is interesting to note that the subcellular distribution of norepinephrine in the caudate nucleus (rat) is different from that of dopamine. This can be concluded from the observation (113) that, after uptake of H^3-dopamine from the lateral ventricle, the ratio "particle-bound amine to amine in the supernatant" in the caudate nucleus was higher for the (newly formed) H^3-norepinephrine than for H^3-dopamine. The possibility must therefore be kept in mind that norepinephrine-containing structures may exist in the caudate nucleus which are distinct from those containing dopamine. Although the actual concentration of norepinephrine in this region is very low (215, 241), fluorescence microscopic evidence for the existence of a very labile store of norepinephrine has been presented (71).

When the evidence is considered that most of the dopamine in the striatum is concentrated in nerve terminals, the fact that in this region so little dopamine is particle-bound is surprising. The meaning of this finding is the more obscure since it stands in contrast to what is known about the subcellular localization of other potential transmitter substances found in the brain, like norepinephrine acetyl-choline (155). The possibility therefore has to be considered that the striatal dopamine terminals may possess subcellular characteristics differing from those of other terminals.

D. Metabolism and turnover

1. Formation. The formation of dopamine from L-dopa, its immediate precursor, by the enzyme L-dopa decarboxylase (see fig. 1) has been reviewed by Holtz

(130). This reaction seems to be very efficient and proceeds at a considerable rate. Although there is no strict correlation between the regional distribution of the enzyme and the catecholamines in the brain, it is striking that the highest enzyme activity is present in the caudate nucleus, the hypothalamus, and the mesencephalon (41, 51, 134). The suggestion has recently been expressed that the limiting step in the biosynthesis of dopamine and norepinephrine might be the formation of L-dopa from L-tyrosine by the enzyme L-tyrosine hydroxylase (158). If this is true, no appreciable amounts of L-dopa can be expected to accumulate in the brain tissue. Reports on the occurrence of dopa in brain under physiological conditions (172) may be due to the difficulties which are encountered when assaying chemically dopa in the presence of other dihydroxyphenolic compounds.

It is interesting to observe that after administration of some centrally acting drugs like morphine, β-tetrahydronaphthylamine, or oxotremorine, the concentration of the dopamine metabolite homovanillic acid in the caudate nucleus increases considerably (157) since in all these instances the concentration of dopamine in this tissue remains unchanged. If we assume that the above compounds increase the concentration of homovanillic acid by accelerating the utilization of dopamine in the tissue (243), the unchanged dopamine concentrations can be taken as evidence of a very rapid rate of formation of dopamine in the caudate nucleus. This is in contrast to the behavior of norepinephrine since all the drugs mentioned lower its concentration in the hypothalamus (157, 241), probably because resynthesis of the amine from dopamine is slow.

The studies on the rate of formation of dopamine and norepinephrine from the precursor amino acids, both *in vitro* and *in vivo*, have been most informative. Large amounts of dopamine were formed in slices of caudate nucleus, but not in other areas of the cat brain, on incubation in a medium containing L-tyrosine-C^{14} (165, 169). In contrast, little (169) or no (165) norepinephrine was formed in this brain region from L-tyrosine-C^{14} *in vitro*. The latter finding has been confirmed *in vivo* by Glowinski *et al.* (112). These authors were able to show that, after introduction of H^3-dopamine into the lateral ventricle of the rat, the amine was easily taken up by the caudate nucleus and other brain areas. However, in contrast to the other brain areas, where 30 to 50 per cent of H^3-dopamine was converted to H^3-norepinephrine, only small amounts of H^3-norepinephrine were found in the caudate nucleus.

The reported studies demonstrate that in the striatum the metabolism of norepinephrine has quite different biochemical characteristics from that of dopamine and lend additional support to the possibility already discussed (see this Section, C) that in this region the two amines might be localized in separate structures.

The fact that there is a high rate of formation of dopamine, but not norepinephrine, from the precursor substances is puzzling in view of the finding that the activity of the enzyme dopamine-β-hydroxylase, which is responsible for the conversion of dopamine to norepinephrine, is high in the caudate nucleus (236). However, the authors measured the enzyme activity *in vitro*, fortifying the enzyme preparation with all necessary co-factors. In contrast to this finding, the

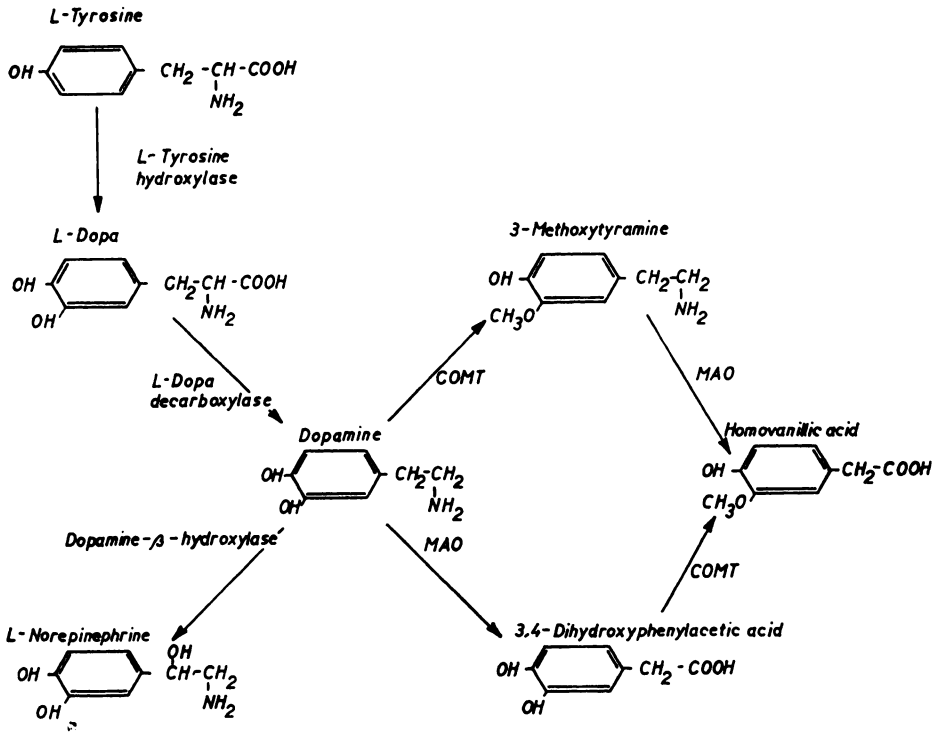


FIG. 1. Main pathway of biosynthesis and catabolism of dopamine in the mammalian organism. L-dopa: L-dihydroxyphenylalanine; MAO: monoamine oxidase; COMT: catechol-O-methyltransferase.

evidence mentioned above indicates that the actual activity of the enzyme in the caudate nucleus *in vivo* is low. It has to be assumed then that either the dopamine and the enzyme are localized in separate compartments of the striatal cell or that there exists *in vivo* a lack of some factors necessary for full activity.

2. Catabolism. The main metabolic break-down product of dopamine in the brain is homovanillic acid (4-hydroxy-3-methoxyphenylacetic acid; see fig. 1). The occurrence and regional distribution of this dopamine metabolite in the brain has already been discussed (see this Section, A). In the formation of homovanillic acid at least two enzymes are known to be involved, monoamine oxidase (49) and catechol-O-methyltransferase (13). Evidence has been presented that in the brain most of the dopamine formed from exogenous L-dopa is first attacked by monoamine oxidase, leading to formation of 3,4-dihydroxyphenylacetic acid, the latter compound being then O-methylated to produce homovanillic acid (9, 59). The occurrence in the brain of small amounts of 3,4-dihydroxyphenylacetic acid was reported for the first time by Euler in 1958 (88). Rosengren (194) showed that the regional distribution of this compound in the brain was similar to that of dopamine. Recently, the occurrence of 3-methoxytyramine in the

brain has been reported (64). This finding is important as it indicates that small amounts of brain dopamine might undergo O-methylation before oxidative deamination. The concentration of 3-methoxytyramine in the brain increases considerably under the influence of inhibitors of monoamine oxidase (64).

3. Turnover. All available evidence indicates that brain dopamine is turned over at a high rate. This conclusion was reached from experiments showing that in rats injection of harmine, a quick-acting inhibitor of monoamine oxidase, made the dopamine content of the brain rise significantly within 10 to 20 minutes (135). This finding suggested that the turnover of brain dopamine, while comparable to that of brain 5-hydroxytryptamine (237), is distinctly higher than that of brain norepinephrine. According to Vogt (243) the occurrence of relatively high concentrations of the dopamine metabolite homovanillic acid in the dopamine-rich parts of the brain, as contrasted by the very low concentration of acid metabolites of norepinephrine, can also mean that dopamine is being turned over at a faster rate than norepinephrine in the brain. This view is substantiated by the finding that H^3-norepinephrine taken up *in vivo* from the lateral ventricle of rats disappears relatively slowly from the striatum, and relatively small amounts of metabolites of H^3-norepinephrine accumulate in this structure (113). A further finding illustrating the high speed of dopamine turnover is the ease with which several drugs (morphine, β-tetrahydronaphthylamine, oxotremorine, phenothiazine derivatives) increase the homovanillic acid and 3-methoxytyramine concentrations in the caudate nucleus of different species (10, 32, 61, 157).

Recently, Glowinski *et al.* (113), measuring the relative rates of disappearance of H^3-dopamine and H^3-norepinephrine from the striatal tissue after the amines had been taken up from the lateral ventricle *in vivo*, found dopamine to disappear at a faster rate than norepinephrine. This fairly direct approach to the study of the *in vivo* rate of dopamine turnover in the striatum very strongly argues in favor of a high turnover rate of dopamine, but not norepinephrine, in this part of the brain.

E. Neurophysiological activity

1. Lower animals. Despite the possibility that dopamine effects in *Crustacea* may lack any physiological significance, as the amine has not been detected in this species, findings reported by McGeer *et al.* (171) deserve special consideration. The authors showed that on the stretch receptor neuron of the crayfish, *Pacifastacus leniusculus* (*Dana*), dopamine had the highest inhibitory activity of all substances tested. On this preparation dopamine was about 60 times more potent than γ-aminobutyric acid, and at least 10 times more potent than *d,l*-norepinephrine, *l*-norepinephrine or *l*-epinephrine. The authors presented evidence for the view that, in crayfish stretch receptor neuron, dopamine and γ-aminobutyric acid may act on two different types of receptor. They found that, whereas picrotoxin blocked the activity of γ-aminobutyric acid to a great extent, it was only weakly effective against dopamine. On the other hand, chlorpromazine and dibenzyline were ineffective against γ-aminobutyric acid but blocked the action of dopamine almost completely.

Using different crayfish species, other workers (see 177) failed to confirm the above findings. The divergencies could possibly be explained by the finding (177) that, of four crayfish species, dopamine was active only in *Pacifastacus leniusculus* and *Procambarus blandingi*. γ-Aminobutyric acid was active in all four species.

In view of the lack of evidence that dopamine may actually be present in the nerve cells of crayfish, the possibility must be kept in mind that the remarkably strong inhibitory action of the amine on the stretch receptor neuron may be unrelated to any physiological role of dopamine.

Electrophysiological findings obtained in molluscs deserve special consideration because of the well established occurrence of dopamine in the nervous tissue of many members of this phylum (see this Section, A).

Kerkut and Walker (146, 147) measured the effect of potential transmitter substances on the resting potential and the spontaneous action potentials of the nerve cells of the brain (isolated and *in situ*) of the common garden snail *Helix aspersa*. The results of these studies showed clearly that the overall physiological action of dopamine was to inhibit the activity of some nerve cells. Of all the substances tested, dopamine was the most potent in causing hyperpolarization of the nerve membrane (effective concentration: 10^{-11} g dopamine/ml). It is of special interest that, in contrast to dopamine, norepinephrine and epinephrine had either mixed (excitatory or inhibitory) or purely excitatory effects, and that the effective concentrations of these amines were considerably larger than those of dopamine.

Recently, comparable observations have been made by Gerschenfeld (108), who studied the action of various agents on the neurons of the ganglia of the Argentine land snail, *Cryptomphallu aspersa*. Here again, dopamine had a constant strong inhibitory action on the so-called "D cells with inhibition," the effective concentrations being relatively low (10^{-9} M). Other potential transmitter substances had no comparable inhibitory effect.

2. Mammals. Curtis and Davis (73) were the first to show that, when applied iontophoretically to the lateral geniculate nucleus of the cat, dopamine and some other compounds suppressed the orthodromic responses of single neurons responding to an optic nerve volley. Dopamine was more potent in this respect than norepinephrine and epinephrine; 5-hydroxytryptamine had the highest inhibitory potency in this preparation.

In a study in which several compounds were tested on single neurons in the cerebral cortex of cats by iontophoretic release from micropipettes, dopamine exhibited a depressive action on the neuronal discharge initiated both by synaptic activity and by application of L-glutamate (152). Again, dopamine was more potent in this respect than epinephrine. Similarly dopamine is more potent than norepinephrine in inhibiting single neuron activity in the hippocampus of the cat (123). Observations made on individual neurons of the caudate nucleus and the putamen of the cat (50) and rabbit (123a) showed that iontophoretically administered dopamine inhibited both the spontaneous cell activity and the activity induced by L-glutamate and DL-homocysteic acid. It seems of special

physiological significance that the amine also inhibited the discharge of single caudate units induced by electrical stimulation of the nonspecific thalamic nuclei (123a).

Conflicting results have been reported on the action of topically applied dopamine on the activity of spinal cord neurons. The discrepancies bear a strong resemblance to the controversial findings concerning the occurrence of the amine in this part of the central nervous system (see this Section, A2). McLennan (174) reported that application of strong solutions (2.5 to 5 per cent) of dopamine to the exposed spinal cord of the cat inhibited the monosynaptic reflex arc. In a later study, the author suggested (175) that dopamine excites inhibitory interneurons which make synaptic contact with the motoneurons of the cord. However, when applied iontophoretically to various types of spinal cord neurons of the cat, dopamine completely failed to display any inhibitory action on interneurons, Renshaw cells, or motoneurons (72). According to Curtis (72) the latter findings make it unlikely that the amine plays a physiological role as an inhibitory transmitter in this region of the central nervous system.

Summing up the observations concerning the neurophysiological activity of dopamine, it is interesting to note that the most consistent effect of the amine on the activity of single neurons of the brain is inhibition, both in lower animals and in mammals. To the writer, this uniformity of action in species so different as snail and cat seems of special significance. In this connection the fact seems puzzling that in experimental animals dopamine affects motor activity to produce what can only be described as central excitation (see Section IV A). However, it should be kept in mind (a) that it is not unlikely that dopamine causes excitatory effects at some sites of the central nervous system and inhibition at others (see 243), this being a possibility in the periphery for all catecholamines, and (b) that it is well known that increase of activity of the central nervous system may result not only from a direct positive action on the activity of excitatory neurons but also from depression of inhibitory neurons. Thus overall effects of a given compound on the central nervous system do not allow any definite conclusions to be drawn as to its neurophysiological mode of action.

Concluding this section, one finding should be mentioned which, if confirmed, would be of fundamental importance. McLennan (176) reported experiments performed in cats showing that increased amounts of dopamine were released in the caudate nucleus upon electrical stimulation of the nucleus centralis medianus of the thalamus. From this finding, the author assumed the existence of nerve cells in the caudate nucleus which are directly excited by the nucleus centromedianus of the thalamus [fiber connections between these two nuclei are well established (69)], and whose terminals release dopamine upon other caudate neurons. At present, however, this important observation can not be reconciled with two other findings. (a) Most, if not all, dopamine-containing terminals in the caudate nucleus are assumed to belong to neurons originating in the substantia nigra (see Section III B); yet McLennan found no increased release of dopamine in the caudate nucleus when in one of his experiments he accidentally

stimulated the substantia nigra.[1] (b) From what we know about the cytology of the caudate nucleus (see 69), the neurons assumed by McLennan to release dopamine most probably belong to the population of the numerous small caudate nerve cells. Yet no decrease of the dopamine content of the caudate nucleus was found in Huntington's chorea (81), an illness known to be associated with degeneration of the majority of the small caudate neurons. Despite these objections, the writer feels that we cannot disregard the possibility proposed by McLennan, unless we have direct proof to the contrary.

IV. CENTRALLY ACTING DRUGS AND BRAIN DOPAMINE

Several centrally acting drugs affect the formation, storage and metabolism of dopamine in brain. Many of these compounds lack specificity, since they also affect the brain norepinephrine. Therefore, studies in which central effects of such drugs are being correlated with their effects on the metabolism of one of the two catecholamines have to be treated with caution, and care taken when interpreting the results. The writer feels that, in a strict sense, one would be entitled to correlate the effects of drugs influencing the functions of the extrapyramidal motor centers only with their effects on the dopamine metabolism in the nigro-striatal complex. To adhere to this definition too strictly would, however, exclude from consideration a great deal of important, though mostly indirect, evidence on the possible role of dopamine in brain function. There is therefore no need to disregard such evidence as long as one keeps in mind their proper, that is to say limited, meaning.

A. L-Dihydroxyphenylalanine (L-dopa)

1. Motor activity and brain dopamine. The actions of DL- and L-dopa on the activity of the central nervous system in different animals (mouse, rat, rabbit, cat, monkey) have been studied by several investigators (48, 94, 179, 217, 219, 220, 239, 249). Most authors agree that doses of dopa ranging from 100 mg to 1 g/kg produce marked stimulation of the locomotor activity accompanied by behavioral changes of the treated animal. About 30 minutes after the injection of dopa the animals, apart from being hyperactive, show increased irritability and aggressiveness; they fight with each other; they no longer congregate in a group, but prefer isolate positions. With high doses (500 mg/kg or more) of dopa, autonomic signs like piloerection, salivation, hyperpnea, pupillary dilatation, blanching of the ears, urination, defecation and ejaculation may be observed. Straub's tail-raising phenomenon is very common. "Catatonic" postures and "fear" reactions have also been described. In contrast to these observations, Smith and Dews (218) found that DL-dopa (100 mg to 1 g/kg) suppresses locomotor activity in normal mice. In mice pretreated with a monoamine oxidase

[1] After completion of the manuscript of this article, McLennan (176a) reported that, in cats, stimulation of the substantia nigra was accompanied by an increased liberation of dopamine in the putamen. This finding conforms well with the concept of dopaminergic nigro-striatal neurons.

inhibitor, these authors, like many others, observed a marked enhancement of spontaneous motor activity after dopa.

The varied phenomena following administration of dopa to animals show that it is almost impossible to relate all these effects to a common cause and a single site of action. As dopa is believed to be pharmacologically inert, it is conceivable that some of its effects are in fact the actions of the amines formed from it at different central and peripheral sites of the body. In the brain L-dopa is converted to dopamine (63), and, to a lesser extent, to norepinephrine. Also the concentration of the acid metabolites of dopamine (3,4-dihydroxyphenylacetic acid, homovanillic acid) increases considerably in the caudate nucleus following administration of L-dopa (9, 59). The rate of accumulation of the newly formed catecholamines (particularly of dopamine) roughly parallels the regional distribution of the endogenous catecholamines (40, 187). Thus, the highest amounts of dopamine formed from DL-dopa were found in the striatum about half an hour after the injection of the drug (40). Some of the central effects of dopa may well be due to the largely increased dopamine level in the extrapyramidal centers of the brain. This assumption is supported by the close time correlation which seems to exist between the effects of dopa on behavior and on brain dopamine. Both effects reach their maximum about 30 minutes after injection of dopa.

Everett and Wiegand (94) performed experiments devised to correlate as a dose-response curve the relation of brain catecholamines to increasing degrees of motor behavior and aggressiveness of mice. In order to obtain a series of gradually increasing degrees of motor activity, reactivity and aggressiveness, the authors combined a constant dose of L-dopa (100 mg/kg) with different doses of a monoamine oxidase inhibitor (pargyline), the latter being given 3.5 hours prior to L-dopa. Under these experimental conditions the various degrees of motor hyperactivity were paralleled by gradually increasing amounts of brain dopamine (4- to 12-fold above the control level). The levels of brain norepinephrine did not change significantly except in the animals with very marked behavioral changes, the concentration of norepinephrine in these cases being about 50 per cent higher than normal. It is important to note that small increases of brain dopamine (double the control level) were usually found to be without effect on the behavior of the animals (94).

Similar conclusions may be drawn from experiments on the *anti-reserpine effect of dopa*. It has been noted by serveral authors (48, 62, 94, 218) that dopa restores to normal the greatly decreased motor activity induced by reserpine or reserpine-like drugs. The anti-reserpine effect of dopa is greatly potentiated by monoamine oxidase inhibitors. Under these experimental conditions again a large increase of the level of dopamine in the brain was found, the level of norepinephrine increasing to normal value only (94). Everett and Wiegand (94) believed that these results strongly support the idea of an important role for dopamine in motor activity.

The fact that in reserpinized animals dopa was at least as potent as in normal animals in causing motor hyperactivity is worthy of special attention as it shows

that brain norepinephrine is not decisively involved in this dopa action on the central nervous system. This follows from the fact that in reserpinized animals less norepinephrine is formed from dopamine than in normal animals because of the reserpine-induced inhibition of uptake of dopamine into the sites of norepinephrine synthesis. So far this has been shown to be true for peripheral tissues only (149, 150) but there is no reason to doubt that it also holds good for the brain.

2. Electroencephalogram and brain dopamine. Administration of dopa to rabbits, cats and monkeys causes an "arousal reaction" in the electroencephalogram (92, 148, 162, 179). Recent evidence suggests that this dopa effect may be more closely related to the increase of dopamine in certain areas of the brain than to an increase of brain norepinephrine. In anesthetized cats infusion of L-dopa (5 to 20 mg) into the carotid artery on one side caused an activation of the electrocorticogram which was confined to the side of infusion (74). Under these conditions the norepinephrine content of hypothalamus and midbrain reticular formation was unchanged. In contrast, the dopamine content of the caudate nucleus was often more than doubled on the side of infusion; in the hypothalamus and midbrain reticular formation of the treated side the dopamine concentration was also increased by a similar proportion, although the absolute amounts of newly-formed dopamine in the latter regions were correspondingly lower than in the caudate nucleus. From this it was concluded that the unilateral effect of dopa on the electrocorticogram might possibly be related to the increased dopamine concentrations either in the caudate nucleus or the reticular formation. To the writer the caudate nucleus seems the more likely site of action in this particular case. He bases his view on the experience that unilateral electrical stimulation of the reticular formation invariably results in activation of the electrocorticogram on both sides of the brain (227); the same would hold for the reticular activation by dopa or by dopamine formed from it. It has been stated that the caudate nucleus can exert an effect on the arousal mechanisms (125), but this has been questioned recently (154). It should be mentioned here that, in contrast to all other investigators, Costa *et al.* (67) observed no electroencephalographic changes in rabbits after intracarotid injection of dopa.

The above results are noteworthy because they represent an attempt to correlate a well defined effect of dopa (activation of the electrocorticogram) with changes of catecholamines in different parts of the brain. As has already been shown for the behavioral effects of dopa, the above experiments strongly suggest that the activating effect of L-dopa on the electrical activity of the cortex is more likely to be mediated by the dopamine than by the norepinephrine formed from the amino acid in the brain.

In conclusion, it may be said that, on the whole, experiments with dopa furnish only indirect evidence for a role of dopamine in brain function. This, however, is mainly due to our lack of knowledge concerning the participation of the extrapyramidal centers in the behavioral states induced by dopa, *e.g.*, motor hyperactivity, aggressiveness, electrical activity of the cortex, *etc.* From recent findings it may be concluded that this in fact may be the case since compounds like morphine, β-tetrahydronaphthylamine, and oxotremorine markedly increase

the concentration of homovanillic acid in the caudate nucleus of different species (157), probably by increasing the metabolism of dopamine in this tissue (243). As all these compounds induce behavioral changes connected with greatly increased motor activity of the animals (157), the analogy to the central biochemical and behavioral effects of dopa is striking. The findings concerning the central effects of dopa do show that some of these effects are more likely to be mediated by the newly-formed dopamine than by norepinephrine. Since, however, in regions other than the striatum (*e.g.*, hypothalamus) substantial amounts of norepinephrine are formed from precursor substances (113, 165, 169), the possibility has to be seriously considered that some effects of the administration of dopa may be due to the increased formation of norepinephrine in these parts of the brain. This may especially be true for signs of increased activity of the central representations of the sympathetic system.

Effects of L-dopa on the reflex activity of the spinal cord have been reported recently (7, 8). As long as the occurrence of dopamine in the spinal cord has not been established unequivocally, the proper significance of the reported dopa effects cannot be assessed.

B. Reserpine

In contrast to many other drugs which act on brain dopamine, reserpine possesses clear-cut actions on the functions of the extrapyramidal centers. In animals, the drug induces a state of rigidity and akinesia. These actions largely contribute to what is commonly called a reserpine-induced catalepsy (see 23). Tremor is also a frequent sign of reserpine action. In man, even more clear-cut extrapyramidal symptoms can be observed, as longer lasting treatment with reserpine is known to produce a syndrome indistinguishable from that seen in Parkinson's disease and postencephalitic parkinsonism. In this syndrome extrapyramidal signs with rigidity, tremor and akinesia predominate. The remarkable similarity of the reserpine-induced state and the genuine parkinsonism is very informative. It has been known for a long time that human parkinsonism is mainly due to a dysfunction of certain extrapyramidal centers, *i.e.*, substantia nigra, striatum and pallidum (see 143).

Reserpine depletes the brain of its dopamine content (63), causing a deficiency of the amine in the striatum and the other dopamine-containing regions (substantia nigra, pallidum). The idea suggests itself that the extrapyramidal symptomatology induced by reserpine both in animals and in man is the consequence of the dopamine deficiency in the extrapyramidal centers (39, 57). It is true that reserpine also depletes the brain of its norepinephrine and 5-hydroxytryptamine, but biochemical evidence already discussed (see Section III D) indicates that norepinephrine is unlikely to play any major part as a neurohumor in the striatum. In contrast, the possibility should not be overlooked that 5-hydroxytryptamine in the extrapyramidal centers may be involved to some extent in the reserpine actions in question (see below and Section V B).

The following findings suggest an intimate relationship between the extrapyramidal effects of reserpine and its action on brain dopamine:

1. Catalepsy and hypokinesia. Reserpine-induced catalepsy in animals and

hypokinesia in animals and in man are readily counteracted by administration of dopa (48, 62, 77, 93). In this respect, 5-hydroxytryptophan was without effect, although combination of the 2 compounds gave the best results (62). This shows that 5-hydroxytryptamine may in fact possess a hitherto unrecognized action on the extrapyramidal functions. It is especially noteworthy that the motor hyperactivity achieved by dopa in combination with a monoamine oxidase inhibitor was even greater in animals pretreated with reserpine. (The significance of this finding has been discussed in this Section, A.)

2. Rigidity. The reserpine-induced rigidity in rats is accompanied by a concomitant increase of α-motoneuron activity and a decrease of the γ-fiber activity (226). This reserpine effect is believed to be of supraspinal origin (193). Injection of L-dopa not only abolished the rigidity and tremor but also reversed the reserpine effect on the α- and γ-fibers; the effect vanished 40 minutes after injection (193). 5-Hydroxytryptophan had an effect somewhat similar to that of dopa.

3. Conditioned behavior. It is well known that reserpine depresses conditioned reactions, especially the conditioned avoidance response (see 79). Again, this reserpine effect can be antagonized by dopa in rats and mice (208, 209) and in cats (210, 244). This dopa effect was paralleled by an increase of the lowered brain dopamine concentration to a level above normal. The norepinephrine concentration remained subnormal. Similar results (120) have also been obtained in rats and cats treated with α-methyl-*p*-tyrosine. This compound has recently been shown to deplete the tissues of their catecholamine content by inhibiting the enzymatic formation of L-dopa from L-tyrosine (181, 223).

In this connection the finding should be mentioned that the potency in depressing the conditioned avoidance response by phenothiazine derivatives is correlated best with their cataleptic potency (229, 230). This is by no means surprising, as extrapyramidal dysfunctions like rigidity and akinesia caused by phenothiazine derivatives must be expected to have an inhibitory effect on the motor performances of the animals. It is thus tempting to assume that the same may hold good for the reserpine-induced depression of the conditioned avoidance response. If such were the case, the restoration by dopa of the disrupted avoidance behavior would simply represent another example of the evidence that extrapyramidal effects of reserpine are specifically antagonized by increasing the lowered concentration of brain dopamine. The above suggestion should, however, not be interpreted to mean that reserpine has no specific effects on the conditioned behavior; the latter might be quite independent of its effects on the extrapyramidal system and dopamine.

4. Convulsions. Reserpine lowers the threshold for electroshock- or pentylenetetrazol-induced convulsions (65). An extensive study in rabbits pretreated with reserpine showed that increase of the lowered level of brain dopamine by administration of dopa and a monoamine oxidase inhibitor raised the lowered threshold for electroshock to values 3 times the normal level (202). The threshold-increasing effect of amphetamine in reserpinized rabbits was also increased by administration of dopa (202). In normal mice, combined administration of

dopa and a monoamine oxidase inhibitor elevated the threshold for pentylentetrazol-induced convulsions (151); 5-hydroxytryptophan given with the inhibitor also had this effect (151). All these results suggest that the threshold-lowering effect of reserpine for convulsions might be causally connected with the depletion of brain dopamine. It should be remembered, however, that Prockop *et al.* (191) could find no effect of dopa on the threshold for electroshock-convulsions in mice pretreated with iproniazid or reserpine.

Most of the results discussed in this subsection seem to indicate that a correlation exists between the reserpine-induced dysfunctions of the extrapyramidal centers of the brain and the concomitant decrease of their dopamine content. The findings about the role played by reserpine or dopamine for the threshold in electroshock- and pentylentetrazol-convulsions require a special comment. There is experimental evidence that the striatum has some restraining functions controlling the level of excitability of the cerebral cortex as a whole (143). This seems to follow from the finding that stimulation of the caudate nucleus (cat) inhibits the seizure activity in other brain structures (234). In animals with lesions placed in both the cortex and the striatum, epileptic seizures and seizure activity in the electroencephalogram were more serious and longer lasting than in animals with cortical lesions alone (145). Thus, it can be assumed that this influence of the striatum upon the cortical excitability is, in some unknown way, dependent on the presence of normal amounts of dopamine in this region. This assumption would help in understanding both the threshold-lowering effect of reserpine and its antagonization by dopa.

Apart from its extrapyramidal effects, reserpine possesses a range of even more prominent actions on the central nervous system, *e.g.*, the drug influences the functioning of certain autonomic centers, and has a calming effect in animals and in man and anti-psychotic activity in schizophrenic patients. Nothing can be said at present about a possible participation of brain dopamine in these actions of the drug. Although a relationship has been claimed between the extrapyramidal side effects of reserpine (and phenothiazines) and its anti-psychotic activity in schizophrenia (116), there is nothing to suggest that the latter action may involve brain dopamine. In connection with the well known fact that chronic administration of reserpine may produce depressive states in some patients, reports should be mentioned on the beneficial effect of dopa in the treatment of depressive states (142, 233). However, in earlier trials investigators could find no effect of dopa (see 185). It seems impossible at present to decide on the value of these findings. It is also not possible to decide which amine (dopamine or norepinephrine), if either, is the more important one for the claimed anti-depressive action of dopa. About the 3,4-dimethoxyderivative of dopamine and schizophrenia, see Section II A 3.

C. Phenothiazine derivatives

Most phenothiazine derivatives with tranquilizing activity produce rigidity, tremor and akinesia in animals and a Parkinson-like syndrome in man, resembling in this respect very closely the extrapyramidal effects of reserpine.

On the whole, phenothiazine derivatives do not change the concentration of brain dopamine to any great extent (135). Recently, a small, but significant, decrease of dopamine in the caudate nucleus of the cat has been reported for chlorpromazine (157). In contrast, the concentration of the dopamine metabolite homovanillic acid in the caudate nucleus of the cat and rabbit is markedly increased by administration of various phenothiazines (10, 32, 157). This effect seems to be correlated with the potency of these compounds in causing extrapyramidal symptoms (catalepsy) in animals and parkinsonian syndrome in man (32).

In view of the close similarity between the extrapyramidal symptoms caused by reserpine and phenothiazine derivatives, it seems tempting to speculate that both drugs might have essentially the same mechanism of action. Phenothiazine derivatives are known to block the actions of catecholamines in the periphery (68), and the same has been suggested for the brain (53). In support of this hypothesis there are findings showing that phenothiazine derivatives block the central actions of dopa (53), amphetamine (231), and many sympathomimetic compounds structurally related to catecholamines (197, 203). The possibility should therefore not be disregarded that the extrapyramidal actions of phenothiazine derivatives might be caused by blockade of dopamine-sensitive structures in certain brain areas that prevents the endogenous dopamine from acting on its specific receptor. The increased concentrations of dopamine metabolites in the brain after the administration of phenothiazine derivatives could be explained by assuming (61) that the receptor blockade results in a compensatory activation of the specific neurons, triggered by the "functional deficiency" of dopamine. This activation should lead to increased release of dopamine and consequently to increased formation of its acid metabolites. As the resynthesis of dopamine in brain is rapid, the dopamine content itself would remain unchanged. It is worth noting in this connection that phenothiazine-induced parkinsonism in man has been reported to be little benefited by treatment with dopa (168). This might be expected from the view-point of the "dopamine blocking" hypothesis.

It should not be denied that other possibilities exist which may explain the action of phenothiazine derivatives on the dopamine metabolism in brain, especially decreased permeability of the cell membranes for homovanillic acid caused by the compounds in question (10). Activation of synthesizing or metabolizing enzymes can be excluded (82, 111).

Nevertheless, the mere fact that phenothiazines do influence the metabolism of dopamine in the extrapyramidal centers is encouraging. It is hard to believe that the close similarity to the reserpine-induced state (parkinsonism)—the latter being associated with an actual deficiency of dopamine in the extrapyramidal centers—is mere coincidence.

D. Monoamine oxidase inhibitors

Compounds which inhibit the enzyme monoamine oxidase *in vivo* usually increase the monoamine levels in the periphery as well as in brain. Dopamine is

no exception to this rule. Since in most instances the concentration of more than one brain amine is increased after inhibition of the enzyme, the behavioral changes induced by these compounds (increased locomotor activity, *etc.*) cannot with certainty be ascribed to the increase of a single brain amine.

Monoamine oxidase inhibitors potentiate considerably the central effects of L-dopa (see this Section, A), probably by preventing the inactivation by monoamine oxidase of the amines formed from the amino acid. In animals pretreated with an inhibitor, the behavioral changes induced by L-dopa were more closely paralleled by the degree of increase of brain dopamine than of brain norepinephrine (94). These findings have already been discussed in Subsection A of this Section.

E. Miscellaneous drugs

The action of *morphine*, *β-tetrahydronaphthylamine*, and *oxotremorine* on the homovanillic acid content of the caudate nucleus (157) has already been discussed in Section III D.

d-Amphetamine lowers significantly the dopamine content of the caudate nucleus in cats but not in dogs. Concomitantly it raises slightly the level of homovanillic acid in this region (157). As *d*-amphetamine causes alertness and increased motor activity, the idea suggests itself that the behavioral effects of this drug might be mediated, at least partly, by the release of dopamine. Against this possibility is the finding that the central stimulant action of amphetamine remains unchanged after administration of reserpine to the experimental animal (198, 217). The latter finding has been taken as evidence that amphetamine, being chemically related to dopamine, interacts directly with receptors for catecholamines (195, 198).

Cocaine stimulates locomotor activity in animals, and it has been assumed that this effect might be due to release of brain catecholamines, especially dopamine, from their storage sites (195). This seems to follow from the observation that after reserpine, cocaine loses its central stimulating effect (198), whereas dopa restores the effect (195). Since the restoring effect of dopa sets in rather quickly, it has been proposed that the central action of cocaine is more likely to be mediated by release of dopamine than of norepinephrine. This assumption is further supported by the finding that α-methyldopa and α-methyl-*m*-tyrosine, which are known to induce a long-lasting depletion of brain norepinephrine, but not dopamine (60, 124, 190, 221), do not essentially change the central stimulant action of cocaine (195). However, the above assumption is at present not supported by the finding that cocaine does not change the level of dopamine in the rat brain (135) or the concentration of homovanillic acid in the caudate nucleus of the rabbit (32).

V. DOPAMINE AND THE FUNCTIONING OF THE EXTRAPYRAMIDAL CENTERS: SPECIAL ASPECTS

In this Section evidence that dopamine may in fact be involved in the proper functioning of certain extrapyramidal centers of the brain will be discussed.

Most of the pertinent information has already been mentioned briefly elsewhere in this article. In this section, therefore, some special aspects of this question will be discussed in greater detail. A diagram illustrating the relationship of some extrapyramidal centers to each other is shown in figure 2.

A. Human parkinsonism

1. Neurophysiological and neuropathological considerations. The extrapyramidal symptomatology of human parkinsonism (idiopathic Parkinson's disease and postencephalitic parkinsonism) is dominated by rigidity, akinesia and tremor. The neurophysiological mechanisms underlying these symptoms have not yet been established, but it seems safe to state that rigidity and tremor are positive symptoms, caused by an over-activity of certain brain areas. Parkinson's disease and postencephalitic parkinsonism are chronic and degenerative states. This makes the presence of so-called "discharging lesions" in parkinsonism very unlikely (164). It can, therefore, be assumed that the symptomatology is caused by destruction of some definite extrapyramidal area or areas. From this it follows that rigidity and tremor must be looked upon as "release" symptoms, due to a

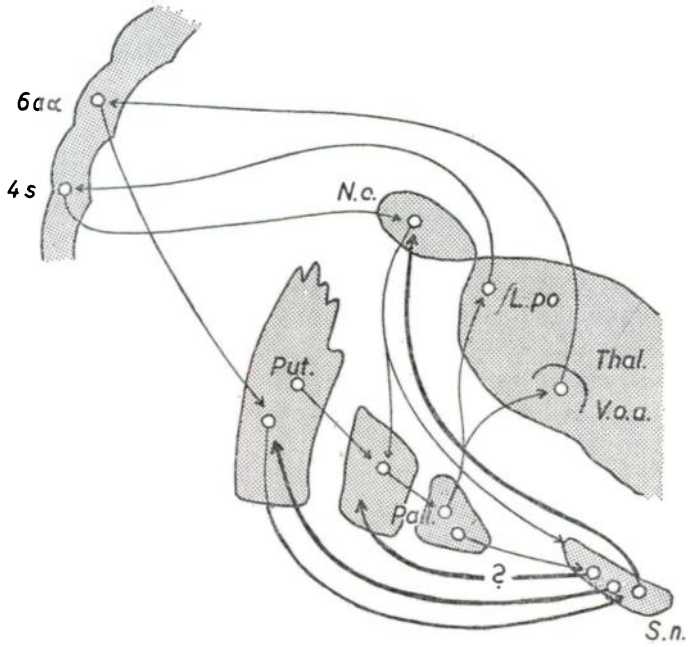


FIG. 2. Diagram illustrating the relationship between the caudate nucleus (N.c.), putamen (Put.), globus pallidus (Pall.), substantia nigra (S.n.), the nucleus ventrooralis (V.o.a.) and lateropolaris (L.po) of the thalamus (Thal.) and the cortical areas 6aα and 4s. Not included into the diagram are: the corpus Luysi and its connections, and the fiber connections between the Thal. and N.c. + Put.; Pall. and hypothalamus; Pall. and the lower brain stem (reticular formation); S.n. and the lower brain stem; cortex and S.n.; cortex and the lower brain stem. — dopamine-containing fibers; —?— fibers assumed to contain dopamine; — fibers probably containing no dopamine.

lack of inhibition normally controlling an excess of function. It is much more difficult to define the true nature of akinesia, which is best defined as "difficulty to initiate voluntary movements."

The most consistent neuropathological finding in human parkinsonism is the degeneration of the melanin-containing nerve cells of the pars compacta of the substantia nigra (122, 143). The cell-loss is most severe and diffuse in cases of postencephalitic parkinsonism, being distinctly milder in idiopathic Parkinson's disease (121). Degenerative changes in other extrapyramidal regions (striatum, pallidum) are probably irrelevant to the parkinsonian symptomatology (122).

It is not at all clear in which way degeneration of substantia nigra induces functional changes in other extrapyramidal regions to produce rigidity and akinesia. It seems clear, however, that these two signs are not causally related to each other, since cases of parkinsonism with nearly pure akinetic symptomatology have often been observed (207).

a. Rigidity. From surgical evidence showing that destruction of the pallidum or its thalamic projections (oral ventrolateral nucleus) makes rigidity and, to a lesser extent, tremor disappear (see 66, 182), the conclusion can be drawn that some inhibitory effect, normally suppressing an excess of activity of the pallidum, is removed by degeneration of the substantia nigra, and that this results in rigidity. Probably this nigral inhibition of pallidal activity is mediated by the nigro-pallidal fiber connections (122, 164), although other pathways cannot be excluded.

b. Akinesia. Akinesia may persist or even increase after pallidectomy (207). To account for the relation between degeneration of the substantia nigra and akinesia the assumption seems unavoidable that normally substantia nigra exerts an enhancing influence upon spontaneous motor activity. In this respect, several possibilities present themselves: (α) Hassler (122) proposed that some of the facilitatory motor impulses originating in the cortex are relayed by way of the substantia nigra to reach the motoneurons, thus enhancing the spontaneous movements. (β) Substantia nigra might enhance motor activity also in an indirect manner, *e.g.*, by modifying the influence exerted on motor performance by the other extrapyramidal regions, particularly the striatum, pallidum, or both. Particularly the striatum has frequently been thought to be concerned with modification of spontaneous motor activity. According to some investigators (see below) the striatum has, generally speaking, a *depressant* effect on spontaneous motor activity. If such is the case, the presumed enhancing action of substantia nigra on motor activity would be due to an inhibitory influence of the latter region upon the striatum. If, however, one assumes that the striatum acts on the cortex to produce *enhancement* of specific motor performances (see below), an enhancing influence of the substantia nigra on that striatal activity would have to be assumed. Either of these opposing possibilities would imply that destruction of substantia nigra would lead to a decreased ability of the individual to perform spontaneous voluntary movements.

There is some neurophysiological and neuropathological evidence to support both of the hypotheses discussed under (β). It is widely assumed that the striatum

is concerned with elaboration of inhibitory impulses which modify the primitive motor pattern of the pallidum in such a way as to permit the performance of purposeful motor activity of the cortex (see 143). It has already been mentioned that the striatum has some restraining functions controlling the level of cortical excitability. This inhibition of cortical activity seems to be an essential condition for the individual to be able to concentrate on specific motor performances (143). On the other hand, other investigators assumed that the striatum normally exerts an inhibitory influence on spontaneous movements. These authors (224, 225) based their view on the finding that prolonged (chemical) stimulation of the caudate nucleus of the cat induced a state characterized *inter alia* by marked reduction of spontaneous movements and reactivity to external stimuli (225). In support of this particular view is the finding that extensive lesions of the striatum induced hyperkinesia in animals and in man (in man: Huntington's chorea) (see 224).

The confusing multitude of possible explanations is, however, not exhausted by the above hypotheses. It must be kept in mind that both the striatum and pallidum probably exert a direct action on the substantia nigra through the fiber connections which exist between these regions (see 69).

2. Neurochemistry. The suggestion that reserpine-induced parkinsonism, and, by analogy, genuine parkinsonism, might be due to dopamine deficiency of the striatum (15, 39, 57) has been substantiated by (a) the observation that parkinsonian patients excrete less dopamine in the urine than normal controls (18, 19) and (b) directly demonstrating a dopamine deficiency in the extrapyramidal centers of patients who had suffered from Parkinson's disease and postencephalitic parkinsonism (81, see also 54). The low urinary values for dopamine in parkinsonian patients have been confirmed by another research group (45). In contrast, the excretion of homovanillic acid in the urine was reported to be normal in parkinsonian patients (115, 199).

Up to now, 40 brains of patients who died of postencephalitic parkinsonism and idiopathic Parkinson's disease have been examined as to their content of dopamine, norepinephrine and 5-hydroxytryptamine. Besides the finding that in all of these cases dopamine was virtually absent from the striatum (27, 28, 30, 31, 33, 81), there was also found to be a decrease of the norepinephrine content of the hypothalamus (27, 81) and of 5-hydroxytryptamine in this and other regions (25). The concentration of these two brain amines was, however, in no case as severely decreased as that of dopamine. The substantia nigra and the pallidum of parkinsonian patients have also been shown to contain subnormal amounts of dopamine (81, 138, 139). Recently, a marked decrease of the dopamine metabolite homovanillic acid in the striatum, substantia nigra and pallidum of parkinsonian patients has been detected (30, 31).

All these neurochemical findings suggest that, generally speaking, there is a decreased ability of the affected brain tissues to form dopamine. However, there also seems to exist in parkinsonism a disturbance of the storing mechanisms for dopamine in the striatum. This follows from the finding that the ratio "homovanillic acid to dopamine" was distinctly higher in the striatum of parkinsonian patients than in normal controls (31). The latter finding could, however, also

be interpreted as meaning that after degeneration of the majority of the dopamine-containing nigro-striatal neurons there occurs a compensatory activation of the still functioning dopamine neurons, which would result in an increase of dopamine metabolism.

Specificity of the dopamine deficiency. The disturbance of dopamine metabolism in the brain of parkinsonian patients seems to differ essentially from the disturbance of the norepinephrine and 5-hydroxytryptamine metabolism. This may be concluded from the finding that the lowered concentrations of the latter two amines in the hypothalamus and other areas of parkinsonian brain were above normal levels in patients treated with monomaine oxidase inhibitors. The dopamine deficiency, however, was not influenced by this treatment (27).

Furthermore, the specificity of the dopamine deficiency of the striatum in parkinsonism seems to be established by the observations that the activity of monoamine oxidase, substance P, and probably also of dopa decarboxylase of this region was found to be within normal limits (26, 29, 33). It is also very significant that in a case of hemiparkinsonism the dopamine depletion was more pronounced in the striatum contralateral to the side of symptoms (22). It should be mentioned in this context that in extrapyramidal disorders associated with an increase of involuntary movements, including Huntington's chorea, the concentrations of dopamine and homovanillic acid in the striatum and pallidum were within normal limits (33, 81). This agrees well with the fact that the amount of homovanillic acid excreted in the urine is also unchanged in Huntington's chorea (200, 250).

Influence of substantia nigra on dopamine metabolism. It has already been mentioned that the destruction of the substantia nigra is much more severe in postencephalitic parkinsonism than in the idiopathic disease. It is, therefore, very significant to find that this morphological difference is reflected by the different degrees of dopamine deficiency of the striatum in these two parkinsonian conditions. As was found earlier (81), and since confirmed by more elaborate studies (28), the deficiency of dopamine and homovanillic acid in the striatum of parkinsonian patients is well correlated with the degree of cell-loss of the pars compacta of the substantia nigra.

In view of this evidence, an influence of substantia nigra on dopamine metabolism in the striatum was postulated (138); moreover, the presence of dopaminergic striato-nigral neurons was suggested (141). Further studies which showed that in Huntington's chorea in spite of the degeneration of the striato-nigral fibers the dopamine content of the substantia nigra was near normal (33) made the latter suggestion unlikely (140). Since it has been shown recently that the main source of striatal dopamine is fiber terminals originating in the substantia nigra (see Section III B), degeneration of these nigro-striatal fibers must be assumed to occur in parkinsonism as a consequence of the destruction of the substantia nigra (5, 76, 188). As the content of dopamine and especially of homovanillic acid was found to be subnormal also in the globus pallidus in parkinsonism, degeneration of nigro-pallidal fibers which might contain dopamine can also be assumed.

Parkinsonian symptomatology and dopamine metabolism. From the neuro-

chemical and neuropathological evidence discussed above the question arises as to the relationship between the parkinsonian symptomatology and the disturbed metabolism of dopamine in certain extrapyramidal regions of the brain. It seems reasonable to assume that such a relationship does in fact exist. The strongest support for this assumption comes, apart from the relation already discussed between the neuropathology and neurochemistry in parkinsonism, from the following two observations: (a) Reserpine mimics not only the symptomatology of the genuine parkinsonism but also the biochemical situation, that is to say, the dopamine deficiency in the extrapyramidal centers. It is hard to believe that this similarity is only coincidental. (b) L-Dopa, which is known to reverse the extrapyramidal effect of reserpine in animals and in man (see Section IV B), also has a beneficial effect on the akinesia and, to a lesser extent, the rigidity of parkinsonian patients (19, 42).[2] The effect of L-dopa on akinesia and rigidity suggests that disturbance of dopamine metabolism may play an important part in both these extrapyramidal dysfunctions. It is, therefore, tempting to speculate that both rigidity and akinesia are caused by loss of nigral influence, mediated by release of dopamine, on the functioning of the pallidum and striatum respectively.

Hypothesis. Summing up the knowledge gained from studies concerned with the metabolism of brain dopamine and the neuropathology of parkinsonism, the hypothesis could be put forward that dopamine may be involved in chemical mediation of (a) nigral impulses leading to inhibition of activity of the pallidum and (b) nigral impulses leading to inhibition (or enhancement) of certain functions of the striatum. From the neurophysiological evidence discussed in Section III E it would appear that dopamine possesses predominantly inhibitory actions on single nerve cells. This would support the view that dopamine causes primarily inhibition of neuronal activity both in pallidum and in striatum.

In this connection it would be interesting to know whether the dopa-induced enhancement of co-ordinated locomotor activity in animals (see Section IV A) could possibly be explained along similar lines. Actually, such a possibility suggests itself when the hypothesis is considered (see this Subsection 1 b) that nigral impulses, mediated by release of dopamine, eliminate the striatal inhibition of spontaneous movements, thus leading to an overall motor activation. According to this hypothesis, increase of dopamine (by dopa) at the level of the striatum would be expected to cause a corresponding depression of the striatal inhibition upon spontaneous movements, that is to say enhancement of motor activity.

The writer emphasizes that the above assumptions are based on neurophysiological over-simplifications, and must therefore be looked upon as representing merely an amendable working-hypothesis. Obviously we are in need of more fundamental knowledge about the neurophysiology of the extrapyramidal system.

[2] This effect of dopa on akinesia and rigidity has been confirmed, with one exception (115), by numerous groups (43, 44, 100, 109, 110, 126, 127, 173, 235). The *therapeutic value* of dopa in human parkinsonism, however, has not yet been definitely established. This, in the writer's opinion, is mainly due to the fact that the unpleasant side-effects of dopa (especially nausea, vomiting, rise or fall in blood pressure) make it practically impossible to inject doses which are high enough to increase the dopamine level sufficiently in the striatum.

It has already been mentioned (see Section II A 3) that the hypothesis has been proposed that 3,4-dimethoxyphenylethylamine, a metabolite of dopamine found to occur in abnormal amounts in the urine of parkinsonian and schizophrenic patients, could contribute to the akinetic rigid syndrome in human parkinsonism. There are, however, at present no direct findings to support such a possibility.

B. Experimental brain lesions in animals

Observations concerned with dopamine metabolism in the extrapyramidal regions (especially the striatum) after lesions in certain areas of the mesencephalon, have been discussed briefly in Section III B. The most complete and informative results in this field are those of Poirier, Sourkes and their colleagues (188, 189, 222). They showed that in the monkey (macacus rhesus, macaca mulatta) lesions of those midbrain areas (ventromedial tegmentum), causing a severe loss of cells in the pars compacta of the ipsilateral substantia nigra, were associated with a low concentration of dopamine and norepinephrine in the corresponding striatum. From this the authors concluded that the pars compacta of the substantia nigra normally exerts a direct influence on the catecholamine concentration of the striatum (188). The animals with low dopamine concentrations in the striatum showed signs of hypokinesia controlateral to the lesion. The results of these experiments in monkeys are directly comparable to, and agree with, the neuropathological and neurochemical work in human parkinsonism.

Fluorescence microscopic evidence suggests that the nigro-striatal dopamine fibers possess characteristics similar to those of other monoamine-containing nerve fibers (6, 76, 106). The amine content of the fiber is very low. Within the striatum typical varicosities appear along the whole length of the terminal fiber, the dopamine content of the varicosities being much higher than that of the fiber. After removal of the striatum, the fluorescence of the fibers increases considerably, and it is now possible to trace the course of the fibers (see below). The latter finding furnishes additional evidence to support the view that these fibers do indeed terminate in the striatal area. Destruction of cortex and thalamus did not change the dopamine content of the caudate nucleus (35).

At present, some discrepancies as to the exact course of the nigro-striatal dopamine fibers seem to exist. All pertinent observations have been obtained from studies in brains with experimental lesions. From fluorescence microscopic evidence in the rat brain, it has been assumed (6, 106) that fiber bundles originating in the substantia nigra run through the ventral part of the crus cerebri, the retrolenticular part of the internal capsule, to enter the striatum *via* the *fibrae capsulae internae*. In the fluorescence microscope no nigro-striatal dopamine fibers have been found in the subthalamus. In contrast, Poirier *et al.* (189) do not think that, in the monkey, nigro-striatal fibers enter and course in the crus cerebri. The authors assume that they accumulate and course above the dorsomedial lip of the substantia nigra as far as the level of the mammillary body, where they are assumed to edge laterally through the subthalamus and the in-

ternal capsule towards the corpus striatum. It is clear that further evidence is needed to settle this question.

In a further study, Poirier *et al.* (189) found that destruction of the most dorsomedial fibers of the cerebral peduncle, causing *per se* no loss of cells in the substantia nigra, was associated with severe depletion of 5-hydroxytryptamine in the striatum. When the corresponding rubro-tegmentospinal tract was also interrupted, Parkinson-like (postural) tremor resulted. This tremor was greatly increased by administration of harmaline to the monkeys.

The possible association of low 5-hydroxytryptamine in the striatum with tremor is worth noting. It has been mentioned above that in human parkinsonism there may be also found a low concentration of 5-hydroxytryptamine in the striatum (25). Excretion in the urine of the main metabolite of 5-hydroxytryptamine, 5-hydroxyindoleacetic acid, has also been reported to be decreased in parkinsonian patients (17), but this finding could not be confirmed by another research group (192 b). The possibility of a connection between the low 5-hydroxytryptamine in the striatum and tremor both in parkinsonian patients and in animals with experimental brain lesions presents an interesting field for study.

The neuropathological and neurochemical studies of the Canadian workers have provided a well-founded experimental basis for further knowledge of the role played by dopamine and other brain amines in the extrapyramidal system.

VI. CONCLUSIONS

The whole body of evidence discussed in this article shows that brain dopamine can be regarded as a strong candidate for a physiologically active substance, regulating the functioning of some extrapyramidal centers, especially substantia nigra, striatum and pallidum. The following findings provide strong support for this view: The dopamine is mainly confined to the extrapyramidal regions mentioned; in these regions, the amine is localized in specific neurons and nerve terminals; its rate of turnover is of a high order of magnitude; is there a correlation between its concentration in the brain and the functional state of the extrapyramidal centers following administration of certain drugs; there is a striking relationship between some extrapyramidal disorders (drug-induced and genuine parkinsonism) and the lack of the amine in the substantia nigra, the striatum and the pallidum; and, finally, that substantia nigra exerts a direct influence on the concentration of the amine in the striatum by virtue of the nigro-striatal dopamine-containing fibers.

In the extrapyramidal centers, dopamine may have either inhibitory or excitatory activity. Neurophysiological evidence obtained in different species points to a predominantly inhibitory activity of dopamine on single neurons of the brain.

Evidence showing that in the retina and in the median eminence (including the pituitary stalk) dopamine may be the predominant catecholamine argues in favor of a specific function of the amine in these brain structures, although there are at present no direct findings to prove this suggestion.

From the evidence discussed in this article a good case can be made for the concept that the physiological activity of the brain dopamine is quite different from that of brain norepinephrine. There are as yet, however, no experiments to positively show that dopamine is a true neuro-transmitter substance in the brain. All central dopamine effects could equally well be explained by assuming that the amine is a modifier of synaptic transmission.

Therefore, in order to establish dopamine unequivocally as a central neurotransmitter substance, there is still one crucial experiment to be done: to demonstrate that upon stimulation of the relevant parts of the brain, dopamine is in fact released at synapses to exert *by itself* an effect on the neurons standing in synaptic relationship with the stimulated dopamine-containing terminals. It is to be hoped that we shall not have to wait too long for this experiment to be performed.

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