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COMMENTARY

FUNCTIONAL AND PHARMACOLOGICAL SIGNIFICANCE OF BRAIN DOPAMINE AND NOREPINEPHRINE STORAGE POOLS

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The concept that multiple pools of stored catecholamines exist in catecholamine-containing neurons has been the subject of research interest for a number of years. The initial observations suggesting the existence of more than one pool came from studies utilizing various methods to determine catecholamine turnover. These methods included determination of decline rates of catecholamines after synthesis inhibition as well as administration of labeled catecholamine or precursor and comparison of the specific activity of released transmitter with that remaining in the tissue. The results of many of these experiments indicated that a non-uniform release of catecholamines occurs and that the most recently stored amine is the first released. Although such experiments are valuable, they do not yield information on the functional roles of apparent multiple pools of catecholamines. The purpose of this commentary is to examine the evidence for the operational significance of transmitter pools in norepinephrine (NE)- and dopamine (DA)-containing neurons of the CNS. The picture that emerges indicates that central DA-containing neurons operate with two distinct transmitter pools, whereas central NE-containing neurons appear to operate with a single functional pool. These considerations appear to dictate pharmacological responses to various dopaminergic and adrenergic drugs.

Neff and Costa [1] showed that, after inhibition of catecholamine synthesis with the tyrosine hydroxylase inhibitor α-methyl-*p*-tyrosine (α-MT), DA and NE exhibit a log-linear decline for several hours. As expected, receptor antagonists or agonists could enhance or inhibit, respectively, the rates of decline. If the catecholamine stores were labeled by administering either radio-labeled precursor or exogenous amines (thus allowing accurate measurements over a short time frame), radio-labeled DA and NE disappeared rapidly for the first 20–30 min, after which disappearance curves similar to those of the endogenous transmitter substances were observed [2–4]. The specific activity of catecholamines released shortly after labeling of the neurons was greater than that remaining in the tissue, but at later times the specific activity of NE or DA released into the medium was the same as that in the tissue [4–6]. Glowinski and co-workers showed that endogenous striatal DA concentrations exhibited a two-phase decline after tyrosine hydroxylase inhibition and that the apparent rapidly disappearing pool represented about 20 per cent of total DA [7]. They obtained similar results with the noradrenergic system using radio-tracer methods [6]. By measuring radio-labeled DA and DA metabolites, Groppetti *et al.* [8] showed that newly synthesized DA was preferentially catabolized, as DA metabolites had a higher specific activity than DA in rat striatum. Recent studies with superfused striatal synaptosomes indicate that DA is taken up and released by two compartment kinetics [9, 10]. Thus, these data suggest that newly taken up or newly synthesized catecholamines are preferentially released over older amine.

Other investigators [11, 12] questioned the validity of some of these experiments. The question arose as to whether a sufficient blockade of tyrosine hydroxylase with α-MT occurred in the earlier-mentioned studies and whether the initial rapid rate of [^{3}H]DA decline might be due to possible metabolites of α-MT such as *p*-hydroxyamphetamine. It was claimed, based on kinetic consideration of the decline rates of newly labeled and endogenous DA, that if two pools of DA exist, then the rapidly turning over pool must be less than 5 per cent of the total striatal DA content (i.e. smaller than experimental error). These reports leave open the significance of the difference in specific activity of released amines that is observed after labeling DA or NE pools.

Functional significance

After Glowinski presented biochemical data favoring multiple pools [5], Carlsson asked whether the phenomenon was an artifact of geometry. That is, amine newly taken up by the neuron would be most likely to enter those amine storage granules adjacent to the neuronal membrane and, conceivably, tyrosine hydroxylase may be organized so as to supply newly synthesized amines to granules juxtaposed with the neurolemma. Thus, NE and DA might not be truly in separate pools, but newly acquired radio-labeled amine would exhibit an initial rapid rate of release because the label would preferentially enter those granules whose contents were most likely to be released first. The question then becomes, is the division of amine content in CNS neurons into apparent releasable and storage pools of any functional significance?

One way to examine this question is to determine whether preferential depletion of readily releasable pools of DA or NE has any behavioral or physiological consequences. A fruitful approach is to examine interactions between catecholamine synthesis

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inhibitors and drugs acting on catecholamine receptors. Chronic administration of α-MT to psychiatric patients greatly potentiates the antipsychotic actions of neuroleptic drugs such as chlorpromazine or thioridazine [13]. These studies demonstrated that long-term inhibition of DA synthesis allows a greater action of DA blocking drugs, but they do not allow interpretation of a prime role for newly synthesized transmitter, since presumably a marked depletion of total DA stores occurs during chronic α-MT administration. Costall and Naylor [14] reported that, in the rat, large doses of α-MT greatly potentiated the behavioral effects (i.e. catalepsy) of the DA receptor blockers. The α-MT was given however, 4 hr before the neuroleptics, a duration which would cause at least a 50 per cent decrease in striatal DA concentrations, thus making difficult any interpretation of the relative roles of storage versus readily releasable pools in DA neuronal function. Shore and Dorris [15] considered this problem by using a short pretreatment with α-MT and examining haloperidol-induced catalepsy. They found that, after only a short exposure to α-MT (30 min), haloperidol-induced catalepsy was quickly and markedly potentiated, even though 80 per cent of the striatal DA content was intact; as small a dose as 10 mg/kg of *d,l*-α-MT (a dose blocking only a small portion of tyrosine hydroxylase activity) significantly increased the catalepsy scores produced by haloperidol. These findings strongly suggested that it was the lack of newly formed DA that allowed the DA receptor blocker to have a greater effect on DA receptors. Biochemical experiments yielded findings in harmony with this idea: α-MT blocked haloperidol's usual ability to raise DA metabolite concentrations and, despite the presence of haloperidol, lowered metabolite levels below those seen in normal animals. Similar biochemical interactions were seen in mesolimbic DA terminal regions [16]. Also in harmony with these effects, systemic injection of α-MT quickly reduces DA concentrations in the hypothalamic–pituitary portal circulation and blood levels of prolactin rise sharply [17]. Similarly, the effects of small doses of haloperidol on operant behavior (including self-stimulation of DA areas) are greatly potentiated by α-MT [18, 19]; behavior can be restored by the stimulant methylphenidate [19] which, unlike amphetamine, is known to release DA from the large reserpine-sensitive pools of DA (see below). These findings indicate that newly synthesized DA has a prime role in the functioning of the DA neuron and that DA probably exists in both a small readily releasable pool and a large storage pool. The rate of exchange between pools is sufficient to maintain normal function in the rat, as α-MT alone does not cause catalepsy until severe catecholamine depletion occurs. The large storage pool, however, cannot supply the needed DA for release following a compensatory demand on the neuron such as that caused by low doses of haloperidol or by direct stimulation via implanted electrodes. Clearly, the presence of DA in separate storage and releasable pools is of important functional significance.

An entirely different picture has emerged from analogous experiments on the noradrenergic system of the rat brain. Pretreatment with α-MT reduces neither NE catabolism nor NE metabolite responses to α-antagonists until at least 40 per cent of brain NE content is depleted [20–22]. Only when NE levels fall below 60 per cent of control do NE metabolite concentrations begin to fall [20, 22]. Franklin and Herberg [23] have reported a rat behavioral model that is in harmony with these biochemical observations. They reported that blockade of NE synthesis by the dopamine-β-hydroxylase inhibitor FLA-63 [bis(4 - methyl - 1 - homopiperazinylthiocarbonyl) - disulphide] did not inhibit intracranial self-stimulation of noradrenergic areas, but that FLA-63 markedly depressed self-stimulation if given to rats pretreated with reserpine 3–5 days before so as to deplete NE stores as well as to block synthesis. Thus, both the biochemical and behavioral evidence suggest that NE stores behave more as a functional unit and that if separate pools of brain NE exist then they must be in rapid equilibrium.

The differences in the functional relationship between storage and releasable pools in the DA versus NE neuronal systems further underscore several fundamental differences in the control of amine synthesis and release. There is evidence that both the DA-containing neurons of the substantia nigra and the NE-containing neurons of the locus coeruleus have autoreceptors on their soma/dendritic surfaces that are inhibitory to impulse flow. For example, iontophoretic administration of DA onto substantia nigra-zona compacta DA neurons or of NE onto locus coeruleus NE neurons inhibits impulse flow of these neurons. These effects are blocked by neuroleptics or α-adrenergic antagonists (preferential for the pre-synaptic α_2-receptor type) respectively [24, 25]. Stimulation of pre-synaptic DA receptors at DA nerve endings in the caudate nucleus is inhibitory to DA synthesis [26, 27] whereas stimulation of pre-synaptic NE receptors decreases the amount of preformed NE released per impulse [28, 29]. Inhibition of impulse flow in NE neurons has little effect on NE concentrations or tyrosine hydroxylase activity in noradrenergic innervated areas [27, 30]. On the other hand, inhibition of impulse flow in DA nigrostriatal neurons by axotomy or γ-hydroxybutyrolactone (GBL) causes a marked activation of tyrosine hydroxylase and increases DA concentrations in the corpus striatum, events seen to a lesser extent in other DA innervated areas [26, 27]. It is believed that inhibition of DA release into the synaptic cleft decreases the DA concentration at pre-synaptic DA receptors that normally are under the influence of DA. The absence of DA at these autoreceptors leads to a disinhibition of tyrosine hydroxylase which, in the face of decreased DA release and metabolism, leads to an elevation of DA neuronal concentrations.

The duration of enzyme activation following cessation of DA impulse flow appears to be dependent upon a functional DA storage system [31]. For example, 3 days after DA depletion by a single injection of reserpine, *in vivo* tyrosine hydroxylase activity is about normal, but the marked enhancement of enzyme activity usually seen after cessation of impulse flow (by GBL) is greatly diminished.

During the many days following DA depletion by a single injection of reserpine, there occurs a gradual and parallel recovery of basal DA concentration (an indication of the return of viable storage granule function) and the recovery of GBL-induced activation of tyrosine hydroxylase. These findings indicate that, during DA autoreceptor modulated activation of tyrosine hydroxylase, the DA storage system serves to sequester DA from tyrosine hydroxylase until a storage saturation point is reached and DA end-product inhibition of the enzyme occurs. This evidence for a biochemical association of tyrosine hydroxylase with the storage granules is in harmony with the apparent localization of tyrosine hydroxylase in proximity to synaptic vesicles in the caudate nucleus [32].

A further example of the differences between dopaminergic and noradrenergic systems is the response of tyrosine hydroxylase activity to amine depletion by a single dose of reserpine. A rapid increase of enzyme activity is seen in the corpus striatum, a DA neuronal terminal region, but the activity is not due to an enhanced amount of enzyme, as shown by immunotitration [33]. Enzyme activity in the striatum returns to normal 3 days after reserpine. In NE areas, an entirely different picture is seen. After reserpine, a marked elevation of tyrosine hydroxylase is seen in the locus coeruleus, an area rich in NE neuronal cell bodies. This elevation is in the form of increased amounts of enzyme protein.

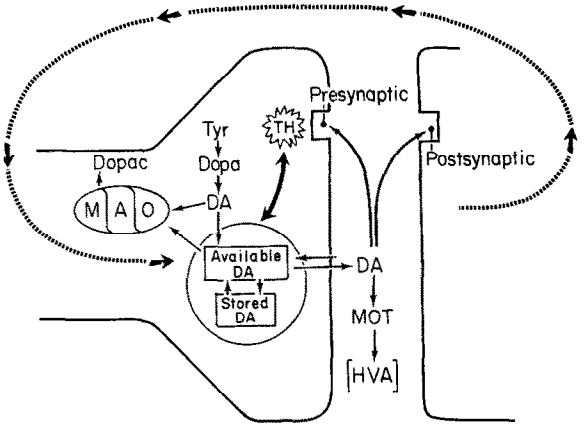

Fig. 1. Intraneuronal flux and control of dopamine (DA) synthesis, release and metabolism. Enzymes: tyrosine hydroxylase, *l*-aromatic aminoacid decarboxylase, monoamine oxidase, aldehyde dehydrogenase, catechol-o-methyl transferase. Abbreviations: tyr, tyrosine; dopa, *l*-dihydroxyphenylalanine; MAO, monoamine oxidase; Dopac, dihydroxyphenylacetic acid; MOT, methoxytyramine; and HVA, homovanillic acid. Besides substrate and co-factor availability and impulse flow, two important regulators of tyrosine hydroxylase activity are occupancy of the inhibitory presynaptic receptor and free intraneuronal DA (i.e. end-product inhibition). The latter is contributed to by synthesis and reuptake and is diminished by catabolism and storage. If release of DA is by exocytosis, then presumably the releasable pool is in synaptic vesicles, but it is not possible to assign the storage pool to a particular ultrastructural component of the DA axonal varicosity.

Enhancement of enzyme activity in NE nerve terminals is very slow and appears to be derived from enzyme reaching terminal areas by axoplasmic flow [33, 34]. As brain NE concentrations slowly return to normal after reserpine, tyrosine hydroxylase activity in the locus coeruleus also gradually declines to normal [33]. The much more rapid alteration in tyrosine hydroxylase activity in DA neurons is consistent with these neurons relying on minute-to-minute transmitter synthesis as a control for release. Tyrosine hydroxylase activity in the DA neuron is regulated by a complex set of controls including: substrate and co-factor availability, end product inhibition, impulse flow, and pre-synaptic receptors [35]. To this list we have added storage granule function. An attempt to summarize these influences is shown in Fig. 1, which presents a conceptualization of a DA neuronal terminal. The two major inhibitory influences on tyrosine hydroxylase in this model are the pre-synaptic autoreceptor and end-product inhibition by free intraneuronal DA. Occupancy of the pre-synaptic receptor will increase as DA release increases. Free intraneuronal DA concentrations are a function of the rates of synthesis, reuptake, and metabolism of DA, and the function of the storage granules. This figure implies that free intraneuronal DA inhibits both the rate of tyrosine hydroxylation and the rate of transfer of DA from storage to releasable sites (see below). Presumably, neurogenic release is by exocytosis [36] and the releasable pool is, therefore, associated with synaptic vesicles [37], but the ultrastructural components of the storage pool(s) are not clear.

Pharmacological significance

The difference in NE and DA storage mechanisms readily explains some of the different effects of drug treatments on these neurons. As already noted, α-MT inhibition of tyrosine hydroxylase causes a sharp drop of DA metabolite concentrations at times when NE catabolism is unaltered. The α-agonist clonidine, which decreases NE impulse flow and release, reduces NE metabolite levels by one-third at 2 hr after administration [38] and the maximal effect is reached at a dose of 0.025 mg/kg. This seems to be the maximal decrease obtainable with clonidine, as a longer time course with a very large dose (0.5 mg/kg) does not cause a further decrease [38]. As shown in Table 1, combining α-MT and clonidine does not produce a much greater decrease of NE metabolite concentrations than does clonidine alone, even though synthesis, as well as impulse flow, is inhibited during the course of the experiment. The effect of monoamine oxidase inhibition with pargyline is shown for comparison and indicates the metabolite level expected if NE catabolism was completely inhibited. The data also indicate that at least half of the NE metabolite concentration (clonidine alone minus pargyline) is unrelated to release of NE and subsequent metabolism, representing nonfunctional metabolism of NE. This inefficient utilization of stored NE may be a consequence of the rapid rate of exchange of NE between storage and releasable pools. On the other hand, DA metabolites drop sharply after α-MT administration, although not as fast as when pargyline is given [41, 42]. Thus, the

Table 1. Effect of clonidine, alone or in combination with α-MT, or pargyline–HCl, on rat whole brain norepinephrine metabolism*

	MOPEG-SO_4† (μg/g)	% Δ
Control	0.157 ± 0.004‡ (20)	
6 hr Clonidine	0.098 ± 0.006 (8)	38
6 hr Clonidine + α-MT	0.071 ± 0.009‡ (8)	55
6 hr Pargyline-HC	0.026 ± 0.008‡ (8)	83

* Rats received 0.2 mg/kg, i.p. clonidine at 0, 2 and 4 hr and were killed 6 hr after the first injection. α-MT (100 mg/kg, i.p.) was injected 5 min before clonidine and an additional 50 mg/kg injected 3 hr later. Additional animals received 75 mg/kg i.p., pargyline–HCl and were killed 6 hr later. Whole brains were removed, frozen on dry ice, and assayed within 24 hr for MOPEG-SO_4 [39, 40]. Numbers in parentheses refer to the number of animals in each group; values are means ± S. E. M.

† 3-Methoxy-H-hydroxyphenylglycol sulfate.

‡ Significantly different from clonidine alone, $P < 0.01$ (Dunnett's *t*-test).

DA neuron conserves its transmitter stores more efficiently. This high level of nonfunctional NE metabolism may explain the apparent lesser ability of α-antagonists to increase NE metabolism compared to the ability of neuroleptic drugs to increase DA metabolism. For example, a 3- to 4-fold increase of striatal DA metabolite concentrations is commonly reported to occur after clinically relevant doses of antipsychotic drugs. In contrast, very large doses of α-antagonists will not even double NE metabolite concentrations [20, 21]. However, if control values are reduced by 50 per cent to better reflect 'functional' metabolism, then the ability of adrenergic drugs to increase NE release and metabolism is more comparable to the neuroleptic drug effects on the dopaminergic system.

The importance of these differences becomes more apparent when the effects of stimulant drugs on DA and NE mechanisms are considered. It is known that behavioral stimulation by *d*-amphetamine is inhibited by pretreatment with α-MT, but not with reserpine [43–76]. Conversely, behavioral stimulation by drugs of the nonamphetamine class (e.g methylphenidate, amfonelic acid, cocaine, mazindol and nomifensine) is inhibited by reserpine pretreatment but not by tyrosine hydroxylase inhibition [45, 47, 48]. These pharmacological interactions are in harmony with the concept of multiple pools in the DA neuron. In single cell recordings from the DA-containing neurons of the substantia nigra (zona compacta), *d*-amphetamine potently inhibits impulse flow, an effect reversed by DA synthesis inhibition with α-MT or DA receptor blockade with haloperidol [49–51]. α-MT, however, does not inhibit the *d*-amphetamine-induced reduction of NE neuronal impulse flow in the locus coeruleus [52, 53]. Apparently, the rapid intraneuronal exchange of NE is able to adequately supply the site of amphetamine-induced NE release. That α-MT inhibits both the behavioural effects and the reduction of DA neuronal impulse flow induced by amphetamine, but not NE neuronal impulse flow, emphasizes the importance of an intact DA synthetic system for the stimulant effects of amphetamine.

Amfonelic acid (AFA) is a potent central stimulant in both rat and man and is of the nonamphetamine class (i.e. inhibited by reserpine). Unlike amphetamine, which reduces both basal and neuroleptic-stimulated DA metabolism in rat striatum [54, 55], AFA alone causes a slight increase of DA metabolism [55, 56]. When combined with neuroleptics such as haloperidol [56] or spiperone [54], a marked synergism occurs, and striatal DA metabolite concentrations increase 3-fold above those seen with neuroleptics alone (10-fold above control concentrations). This effect is dependent upon impulse flow because inhibition of DA neuronal impulse flow with either apomorphine, a DA agonist, or with GBL eliminates the synergistic effects [56]. Furthermore, if small doses of haloperidol which do not prevent the AFA-induced hyperactivity and stereotypy are administered AFA will reduce, rather than enhance, the haloperidol-induced increase of DA metabolism [57], because insufficient haloperidol is present to maintain impulse flow. Thus, AFA seems to enhance the amount of DA released per impulse, and the source of the released DA is the main DA storage pool. Other neuroleptics can substitute for haloperidol, providing that the dose used inhibits AFA-induced hyperactivity. Other nonamphetamine stimulants can substitute for AFA [58]. Among the nonamphetamines there is a striking correlation between central stimulant potency, potency for biochemical synergism with haloperidol, and the ability of these drugs to inhibit DA reuptake by rat striatal synaptosomes [58]. Although the nonamphetamine type drugs are equi-effective in the inhibition of DA uptake by rabbit caudate synaptosomes, these drugs cause little or no CNS stimulation in the rabbit and no synergism with haloperidol on DA metabolism in rabbit brain [59]. The lack of enhanced DA release in the rabbit appears to be due to a DA storage-releasable pool relationship that resembles the rat noradrenergic system described above. Thus, the relationship between storage and releasable pools of DA seen in the rat appears necessary for AFA-induced overflow of DA, and the CNS stimulation by nonamphetamines cannot be explained as the direct consequence of inhibition of DA reuptake. It appears more likely that, secondary to DA reuptake blockade, there occurs mobilization of the large DA storage pool to releasable sites, such that neurogenic release of DA is greatly enhanced [58].

The nonamphetamines also inhibit NE uptake by brain synaptosomes [60–63]. Like the preferential NE uptake inhibitor desipramine, AFA inhibits locus coeruleus impulse flow, an effect which can be reversed by administering an α-antagonist [64]. Neither AFA nor desipramine, however, exhibits a synergistic effect on NE turnover when combined with an α-antagonist [64, 65]; the enhancement of neurogenic transmitter release seen in DA-containing neurons is not seen in NE-containing neurons. Apparently, the rapid exchange between pools of NE, if pools exist, obviates a similar effect of NE uptake inhibitors on NE mobilization. Thus, the differences in storage of transmitter between the dopaminergic and noradrenergic neurons are of considerable importance to the pharmacological sequelae of monoamine reuptake inhibition.

Conclusions

It is interesting that two neuronal systems, which superficially seem anatomically and biochemically similar, are so different in their control mechanisms for regulating transmitter synthesis and release. The apparent principal difference is the dependence of the DA neurons on newly synthesized amine to maintain functional release while the large storage pool remains relatively inert. Thus, DA-containing neurons may regulate release per impulse indirectly by regulating rate of synthesis, while the NE-containing neurons regulate release per impulse directly through pre-synaptic receptors governing release of preformed transmitter. Secondarily, the rate of exchange between storage and releasable pools of DA could be an important point of regulation. DA uptake inhibitors seem to indirectly increase this rate of exchange, allowing much greater release of DA, possibly due to a decrease of free intracellular (newly taken up) DA, with this loss of free DA triggering a rapid rate of exchange between storage pool and releasable sites [58]. Clearly, the intricacies of the DA storage system and local regulation of tyrosine hydroxylase activity represent an integral part of the mechanisms regulating DA release (Fig. 1). On the other hand, such a complex role for storage function is not evident in central noradrenergic neurons, with other mechanisms (e.g. pre-synaptic receptor and impulse flow) regulating the rate of NE release.

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