STORAGE AND METABOLISM OF CATECHOLAMINES: THE ROLE OF MONOAMINE OXIDASE

IRWIN J. KOPIN

Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland

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I. INTRODUCTION

Catecholamines are substrates for an enzyme which is responsible for the deamination of a wide variety of amines. In his comprehensive review, Blaschko (7) discussed the history of the development of knowledge of monoamine oxidase (MAO), its distribution and some of its properties, as well as the role played by this enzyme in the metabolism of a number of naturally occurring and synthetic amines. At that time, and several years later (8), knowledge of the metabolism and disposition of the catecholamines was not well understood and the role of MAO in respect to the catecholamines could not be defined. In 1957, Armstrong *et al.* (1) demonstrated that 3-methoxy-4-hydroxymandelic acid (VMA) was the major metabolite of the β-hydroxylated catecholamines. Shortly thereafter Axelrod showed that O-methylation could precede deamination and that this was the major route of metabolic inactivation of intravenously administered catecholamines. The metabolism of administered catecholamines has been extensively reviewed by Axelrod (2, 3).

The demonstration of the predominant role of catechol-O-methyl transferase in the enzymatic inactivation of circulating catecholamine did not, however, satisfactorily explain a number of other observations, particularly in relation to the effects of drugs which inhibit MAO. More recently, evidence has been presented which shows that there are several pools of bound norepinephrine and that there are differences in the route of metabolic inactivation of the catecholamines, depending on the mode of release from these storage sites. This has provided some insight into the role that MAO plays in the metabolism of the sympathetic transmitter. In this review an attempt is made to summarize what is known about the binding and metabolism of norepinephrine, with particular reference to MAO, and to present a working hypothesis relating the various

bound forms of norepinephrine to each other and to the enzymes involved in its metabolic inactivation.

II. FATE OF CIRCULATING CATECHOLAMINES

A. Metabolism

Axelrod (2), in his excellent review of the metabolism of epinephrine and of other sympathomimetic amines, presented convincing evidence that catechol-O-methyl transferase (COMT) was the enzyme mainly responsible for the metabolic inactivation of epinephrine and norepinephrine, at least following intravenous administration. Orally ingested catecholamines are ineffective in producing the physiological responses seen after intravenous administration. The removal of these substances from blood perfusing the liver is believed to be a very effective process. Since the liver receives a large fraction of the cardiac output, it could play a major role in the metabolism of circulating catecholamines. The effectiveness of liver was demonstrated by the almost complete (80%) inactivation of epinephrine injected into the portal vein (65). More recent studies with radioactive catecholamines have confirmed the fact that a major fraction of intraportally administered catecholamines is inactivated in a single passage through the liver. When epinephrine-H^3 was administered *via* the portal vein, only 2.0% of the radioactivity could be recovered from the urine as unchanged catecholamine; but on injection into a peripheral vein, 13.3% appeared in the urine (41). These results indicate that only about 15% (2.0/13.3) of the catecholamine injected into the portal vein reached the systemic circulation. About one-third of the systemically administered catecholamine was recovered as metanephrine glucuronide, whereas about two-thirds of the epinephrine injected into the portal vein was recovered as the O-methylated metabolite; this result indicates that O-methylation is the major means of inactivation in the liver. From somewhat analogous experiments with intraperitoneally injected norepinephrine-C^{14} and intravenously injected norepinephrine-H^3 it was concluded that only about 30% of the intraperitoneally administered catecholamine reached the systemic circulation unchanged. Use of a COMT inhibitor showed that this enzyme was mainly responsible for the destruction of intraportally absorbed catecholamine (16).

These findings support the view that, at least in the rat, the liver, and perhaps the kidney, both of which contain high concentrations of COMT (5) and receive a major fraction of the cardiac output, may be the organs mainly responsible for the inactivation of circulating norepinephrine by O-methylation.

B. Role of monoamine oxidase

Although norepinephrine is a substrate for MAO, there is considerable evidence that this enzyme does not play a major role in the inactivation of circulating catecholamines. Axelrod has reviewed this evidence (2), much of which is based on the inability of MAO inhibitors to potentiate or prolong the action of administered catecholamines or to slow the rate of their disappearance. He cited, as well, the evidence that COMT is primarily responsible for enzymatic in-

activation of the administered catechols. It is now generally agreed that MAO does not have any major role in the inactivation of circulating catecholamines, except in the deamination of the O-methylated amines formed from the administered catecholamines.

Dopamine can also be O-methylated, but it is a far better substrate for MAO than are the β-hydroxylated catecholamines. Dopamine may therefore be metabolized predominantly by this enzyme.

Most epinephrine seems to originate in the adrenal medulla (28) and it is probably not metabolized to a significant extent before discharge into the blood stream. The fate of intravenously administered epinephrine-7-H^3 would be expected to approximate closely to the fate of endogenously formed epinephrine. This assumption, however, is not valid for norepinephrine. Norepinephrine is present throughout the adrenergic system as well as the central nervous system, and a major portion of this catecholamine could be metabolized before reaching the circulation. That portion of the endogenous norepinephrine which does reach the circulation, however, would presumably be metabolized in the same manner as the norepinephrine administered intravenously.

C. Tissue uptake

Administered norepinephrine-H^3 is not excreted or destroyed immediately. Some of it remains in the tissues for relatively long periods of time in an inactive bound form (45, 84). This binding is markedly decreased in tissues that have been sympathetically denervated for some time (37), and autoradiography has demonstrated that the main binding sites are associated with sympathetic nervous tissue (56). Electron microscopic autoradiography has shown that the radioactivity appears to be localized in the dense-core vesicles of the sympathetic nerve (86), presumably identical with the subcellular particles which have been demonstrated in postganglionic sympathetic nerves (30). When centrifuged in a sucrose density gradient the labeled catecholamine taken up by the rat heart is distributed in the same manner as endogenous norepinephrine (68). Nerve stimulation results in release of the labeled neurotransmitter into the circulation (38, 70), and depletion of labeled and of endogenous norepinephrine by reserpine occurs at the same rate (40). Five hours after the administration of labeled norepinephrine to dogs the specific activity of norepinephrine released from the heart by tyramine and by nerve stimulation is similar to that remaining in the myocardium (18). After the first few hours the labeled catecholamine bound in the tissue appears to be distributed and to behave in the same manner as endogenous norepinephrine.

In these experiments, administered norepinephrine-H^3 was a racemic mixture of the *d*- and *l*-isomers. Only *l*-norepinephrine is present endogenously. Differences in the optical isomers have been demonstrated, and can constitute a source of error in interpretation of experiments in which *dl*-norepinephrine-H^3 is used. One hour after subcutaneous administration, *d*- and *l*-norepinephrine appear in equal amounts in the heart and spleen, but only the *l*-isomer remains 24 hours later (49). Five minutes after intravenous injection, however, only a small

portion of the *d*-isomer is present in the heart (6). The difference in these results appears to be a consequence of selective local binding or metabolism of subcutaneously administered *l*-norepinephrine-H^3, so that much more *d*-norepinephrine-H^3 reaches the circulation than does the *l*-isomer. The extent of binding of the *d*-isomer varies with the administered dose (44a), but, once bound, this isomer is released more rapidly than the *l*-isomer (6, 49). The ratio of *d*- to *l*-norepinephrine may vary with the dosage, the tissue, and time after administration. In most situations, *dl*-norepinephrine-H^3 can be used to label endogenous *l*-norepinephrine, after sufficient time has elapsed to allow the *d*-norepinephrine to be removed. Results obtained in the period immediately after administration of racemic H^3-norepinephrine, however, must be interpreted with caution.

Chidsey *et al.* (19) have shown that about 75% of *dl*-norepinephrine is extracted from the circulation during a single passage through the dog myocardium, so that at least half of the *d*-norepinephrine-H^3 was taken up by this tissue.

These observations and those showing more rapid release of the *d*-isomer than the *l*-isomer may also explain, in part, why tyramine administration and nerve stimulation result in a decrease in the specific activity of norepinephrine released from canine myocardium shortly after the administration of *dl*-norepinephrine-H^3 (18). If, as seems likely, the spontaneously released norepinephrine contains both the *d*- and *l*-isomers, the specific activity of the *d*-isomer would be much higher than the *l*-norepinephrine-H^3, which is diluted by the endogenous catecholamine. Selective release of *l*-norepinephrine by nerve stimulation or tyramine could result in the release of *l*-isomer of the catecholamine having a lower specific activity than the spontaneously released *d*- and *l*-norepinephrine-H^3. After the *d*-norepinephrine has been depleted, the released and myocardial norepinephrine are both *l*-norepinephrine and have the same specific activity.

The importance of inactivation by binding in the tissues becomes apparent when the effects of norepinephrine are studied in the presence of drugs which interfere with the metabolism or binding of catecholamines. When both MAO and COMT are inhibited, the effects of administered catecholamine are potentiated only slightly (21). Procedures which bring about supersensitivity, such as administration of cocaine or chronic sympathetic denervation, are associated with a marked decrease in the capacity of tissue to bind norepinephrine (37, 61, 85). In the isolated perfused rat heart, more than twice as much norepinephrine is inactivated by binding as by metabolism (52). These findings support the earlier suggestion (8, 47) that inactivation by binding at an inactive site may play a major role in termination of the physiological activity of the sympathetic neurotransmitter.

III. TISSUE STORES OF NOREPINEPHRINE

A. Effect of MAO inhibitors

At about the same time that O-methylation was being established as the major means for the metabolic inactivation of circulating catecholamines, other evi-

dence accumulated indicating that MAO does play an important role in the metabolism of endogenous catecholamines. Many drugs have been used as MAO inhibitors. While inhibition of this enzyme cannot prolong the action of administered catecholamines or increase the duration of response to sympathetic nerve stimulation (36, 46), these inhibitors elevate the concentration of the catecholamines in the brain of the rabbit, mouse, and rat (22, 66, 79) and in the hearts of the guinea pig, rat, and dog (22, 60, 67), but not in dog or cat brain (78, 82), other tissues of the cat (29), or rabbit and mouse heart (9, 53). Some MAO inhibitors may have a positive inotropic action, and they actually diminish the norepinephrine content of the heart of the cat (34). The drugs have also been thought to prevent transport of circulating catecholamines into the liver cell (44) and to inhibit the release of catecholamines whether spontaneous or induced by reserpine (4). Hukovic and Muscholl (43) have shown that a rapidly acting MAO inhibitor diminishes the increase in norepinephrine outflow that accompanies nerve stimulation in the isolated rabbit heart. Similar findings have been reported in the cat spleen (24). Thus the *net* effect of a MAO inhibitor on the tissue content of catecholamines may vary with the sum of the effects on the enzyme and on processes involved in transport and storage of the catecholamine. In his excellent review of the release of amines by drugs, Shore (76) has cited the evidence that MAO inhibitors act by inhibition of catecholamine release, as well as by inhibition of the deaminating enzyme; but he concluded that the primary effect of these drugs in increasing tissue amines and in preventing depletion of amines by reserpine is blockade of MAO.

B. Bound forms of norepinephrine

Norepinephrine which is bound in the tissues may be metabolized differently from norepinephrine which enters the blood stream. Consideration of the bound forms of norepinephrine is necessary to an understanding of the roles of the enzymes involved in the inactivation and metabolism of the norepinephrine originating in these stores.

Both pharmacological and biochemical evidence has been accumulating which indicates that there are differences in behavior of portions of the norepinephrine stored in sympathetic nervous tissue. Trendelenburg (81) showed that the diminished responsiveness to tyramine following reserpine administration could not be observed until a large portion of the norepinephrine had been depleted. He suggested that in tissues norepinephrine was present in a small "available" pool which could be released by tyramine and by nerve stimulation and in a larger, "bound" pool which replenished the small pool and could be depleted by reserpine. The multiphasic decrease in norepinephrine-H^3 content of the heart (4) had also suggested a division of the norepinephrine stores in this organ into at least two pools having different turnover rates, and mathematical analysis of the decrease in specific activity of myocardial norepinephrine has been used as a means of estimating the rates of turnover of norepinephrine in these pools (58). Repeated doses of tyramine release only about 60% of the norepinephrine present in the rat heart (69); this finding indicates that the rest is resistant to the action

of tyramine. When tachyphylaxis to tyramine occurs, the heart still contains relatively large amounts of norepinephrine.

Isotopic experiments in isolated tissue or granules have also provided evidence for a division of the norepinephrine stores into more than one pool. Thus, when the isolated perfused heart has taken up *dl*-norepinephrine-H^3, it is released in at least four phases (52). The first, most rapid phase is washout, and the next three progressively slower phases presumably represent release by active transport or from binding sites; possibly there are differences in behavior of the *d*- and *l*-norepinephrine-H^3. An initial rapid uptake of labeled norepinephrine by tissue slices (27) and by granules isolated from bovine splenic nerve (80) can be demonstrated, but isotopic equilibrium is not achieved; and this fact indicates that in these preparations part of the norepinephrine is not readily exchangeable. These pools do not appear to be the equivalent of the norepinephrine present in the soluble and particulate fractions of tissue homogenates (13) since both tissue fractions are depleted by tyramine. Bhagat (5a) has recently demonstrated that before depleting catecholamines from the heart, tyramine shifts the norepinephrine from the particulate to the soluble fraction; later, both fractions diminish at almost equal rates, but complete depletion is not achieved.

Treatment with reserpine results in almost complete depletion of tissue stores of norepinephrine (15) but a small portion of the store remains, and the tissues are still capable of taking up norepinephrine (12, 52, 64). Replenishment of only a very small amount of the catecholamine results in partial restoration of the response to tyramine (23), a result that indicates that the norepinephrine which can be replaced is readily available to the receptor. Since, as noted above, tyramine can deplete 60% of myocardial norepinephrine, the drug must then be capable of releasing two different portions of the norepinephrine stores, one of which is not sensitive to the action of reserpine (33, 50).

Decentralization (42) and acute sympathetic denervation (75, 83) decrease the rate of norepinephrine depletion by reserpine. It has been estimated that in the sympathetic nerves supplying the vasculature in the skeletal muscle of the cat, about 10,000 nerve impulses are required to deplete the norepinephrine of the acutely denervated side to the same extent as on the innervated side (72). These findings indicate the presence in the nerve ending of a pool of norepinephrine which is released by nerve stimulation and appears to be relatively resistant to the action of reserpine. In the rat, after removal of the superior cervical ganglion, reserpine depletion of labeled norepinephrine-H^3 in denervated salivary gland proceeds more slowly than on the innervated side. Tyramine administration will further deplete norepinephrine from both the innervated and denervated sides, but does not decrease the difference between the two sides (32). The difference in norepinephrine content is believed to be the result of retention by the denervated side of catecholamine normally released by nerve stimulation. The fact that tyramine does not eliminate this difference is evidence that this sympathomimetic amine does not release this intraneuronal, reserpine-resistant store of norepinephrine. This conclusion is compatible with the earlier findings that the development of tachyphylaxis to a sympathomimetic amine does not prevent

responses to sympathetic nerve stimulation in the cat nictitating membrane (20), and the observations that in some cats treated with reserpine there is a persistence of the effect of nerve stimulation on the nictitating membrane at a time when there was no response to tyramine or certain other sympathomimetic drugs (10, 62). The ability to restore this reserpine-resistant pool of norepinephrine appears to vary in different tissues and species. Thus, in the hind limb of the reserpinized dog (10), the skeletal muscle of the reserpinized cat (71), and in the nictitating membrane of the reserpinized cat (57), norepinephrine infusion can restore the effect of sympathetic nerve stimulation. In the dog heart Gaffney and Conradi (unpublished observations) found restoration of the cardioaccelerator effect of sympathetic nerve stimulation by single injections of norepinephrine, but not by infusion (see also 5a); the effects of single injections were diminished by subsequent infusions.

Following chronic sympathetic denervation, when the sympathetic nerve endings are presumably degenerated and the tissue norepinephrine is depleted (31), binding of administered norepinephrine-H^3 is greatly diminished (37). The norepinephrine-H^3 which is taken up in the tissue might reflect either incomplete denervation or an extraneuronal store of norepinephrine. If the labeled norepinephrine taken up in denervated tissue behaved differently from norepinephrine bound in sympathetic nervous tissue, this would constitute good evidence for extraneuronal catecholamine binding. *dl*-Norepinephrine-H^3 taken up by the chronically denervated rat salivary gland is not depleted by reserpine (32). Tyramine causes release of a portion of this pool, and cocaine (but not reserpine) interferes with entry of the labeled catecholamine into this storage site. These findings indicate the presence of an extraneuronal store of norepinephrine, resistant to reserpine, but partly depleted by tyramine. The term "extraneuronal" is used only with reference to the sympathetic nerve endings. Reserpine is much less effective in preventing the uptake of labeled catecholamines into the superior cervical ganglion of the rat (Fischer and Kopin, unpublished observations) and it is conceivable that norepinephrine taken up in "floating ganglion cells" in the rat salivary gland may constitute the "extraneuronal" pool. The localization of the site of binding of norepinephrine in denervated tissue must await radioautographic studies.

Entry of norepinephrine into the cell appears to be the result of both diffusion and active transport, since ouabain markedly inhibits the inward flux of labeled norepinephrine (27). In the tissue slices, the rate of exchange of the labeled norepinephrine with the norepinephrine bound in granules appears to be relatively slow. Cocaine inhibits the uptake of norepinephrine *in vitro* (25, 26) as well as *in vivo* (55, 61, 85). Many years ago Burn and Tainter (11) showed that cocaine prevents the sympathomimetic effects of tyramine. Tyramine displaces catecholamines from isolated adrenal granules (73) but this process is not affected by cocaine (74). This led Schümann and Weigmann (74) to suggest that cocaine acts on the cell membrane rather than on the granule. Tyramine and cocaine appear to compete for "transfer sites" associated with active transport of norepinephrine into the cell (33). The dose-dependent nature of this competition

has been cited (13) as a possible explanation for the conflicting reports of cocaine's ability to inhibit the release of cardiac catecholamines by tyramine (39, 54). Indirectly acting sympathomimetic agents appear to have a dual action; they may displace the catecholamines from their binding sites and, like cocaine, they interfere with the membrane (or "transfer site") mechanism for active transport of the sympathetic neurotransmitter back into the cell. This transport mechanism may be the major means of termination of the activity of norepinephrine released from the sympathetic nerve ending.

C. Metabolic fate of bound norepinephrine

In the period immediately following injection of labeled *dl*-norepinephrine, there is a rapid rate of excretion of radioactivity. In man about 8% of the administered radioactivity was excreted during the first 10 minutes. Normetanephrine and its conjugate account for 27% of the excreted radioactivity, and the deaminated catechols for less than 5% (35). In the rat, about 70% of radioactivity administered as norepinephrine-H^3 is excreted in 3 hours, normetanephrine representing more than half of its metabolic products (51). With passage of time there is a decrease in the proportion of total normetanephrine and an increase in relative amounts of deaminated products (35, 51). This suggests that the greater part of the norepinephrine which is transported into the sympathetic nerve endings of various tissues and retained in the storage vesicles is slowly released and deaminated.

After administration of a MAO inhibitor the increase of norepinephrine content in the brain is followed by an increase of normetanephrine, while the catecholamine content remains constant. At the same time the animal becomes excited. These observations led Carlsson (14) to speculate that MAO is close to the site of synthesis and that the rise in normetanephrine indicates release of norepinephrine.

Administration of either reserpine or tyramine results in depletion of at least a portion of the tissue stores of norepinephrine. The adrenergic response accompanying partial depletion of the catecholamine by the action of tyramine is greater than the response accompanying almost complete depletion by the action of reserpine (63). The fate of the norepinephrine depleted by these two drugs was examined in an effort to obtain information about differences in the fate of the "available" or tyramine-releasable portion of the stores and the "bound" portion released by reserpine. Either tyramine or reserpine was administered to animals 10 hours after the administration of *dl*-norepinephrine-7-H^3. As noted above, at this time most of the labeled catecholamine remaining in the tissues is the *l*-isomer and is probably a valid tracer for the endogenous norepinephrine. The increment in radioactivity appearing in the urine of animals treated with these drugs could be expressed in terms of increments in norepinephrine-H^3 and its various metabolites (50). This information was used to calculate the form in which the excreted radioactivity left the tissues. More than half of the radioactivity released by tyramine entered the circulation as norepinephrine and

about one-third as normetanephrine, the remainder presumably having been deaminated in the tissue. After reserpine, only about 15% of the radioactivity was released into the systemic circulation as amines, evidently after deamination of the norepinephrine. From these results it was concluded that the readily released portion of stored norepinephrine was enzymatically destroyed by O-methylation, either in the tissue or after having reached the circulation, whereas the more firmly bound norepinephrine was deaminated. This direct evidence supported the suggestion of Carlsson (14) noted above regarding the relation of MAO and COMT to norepinephrine.

Pretreatment with a MAO inhibitor slowed the rate of release of radioactivity induced by reserpine and resulted in release of unchanged and O-methylated norepinephrine into the circulation, rather than the deaminated products (51). These observations could explain the well-known reversal of the effects of reserpine by MAO inhibitors (17, 66, 77).

In general, drugs which deplete tissue stores of catecholamines without producing marked sympathomimetic effects result in destruction of the catecholamine by MAO within the neurone without release of much active catecholamine (51). Drugs which produce sympathomimetic effects during tissue depletion of the catecholamines result in release of the catecholamines in active form into the circulation, and O-methylation is the major route of metabolic inactivation (51). Nerve stimulation also results in release of norepinephrine and its O-methylated derivative into the circulation (38).

In the isolated perfused rat heart, uptake of norepinephrine into the tissue (presumably sympathetic nerve endings) plays a major role in the inactivation of perfused norepinephrine. O-Methylation is the major means of metabolic inactivation in this preparation. When binding of the norepinephrine is prevented by pretreatment of the animal with reserpine, there is little change in the initial rate of uptake, but the tissue is unable to store the catecholamine, so that what was taken up is then rapidly lost. About one-third of the norepinephrine usually taken up and stored is now taken up and deaminated rather than stored. It may be concluded that binding into the vesicles normally preserves the intracellular norepinephrine transported into the cell by an active process from destruction by MAO. When the storage capacity is decreased by reserpine administration, deamination is increased.

If the primary means of termination of the action of the neurotransmitter is active transport into the cell, the importance of intracellular binding and metabolism may vary with the efficiency of the transport mechanism. When binding and metabolism are blocked by reserpine and a MAO inhibitor, no potentiation of norepinephrine would be expected if transport were very efficient. The fact that MAO inhibitors do not potentiate the effect of norepinephrine in reserpinized guinea pig atria (33) may indicate that in this preparation transport into the cell rather than binding in intracellular particles is the primary means of inactivation of the catecholamine. In the cat, however, reserpine together with the MAO inhibitor, nialamid, does potentiate the pressor effect of norepinephrine,

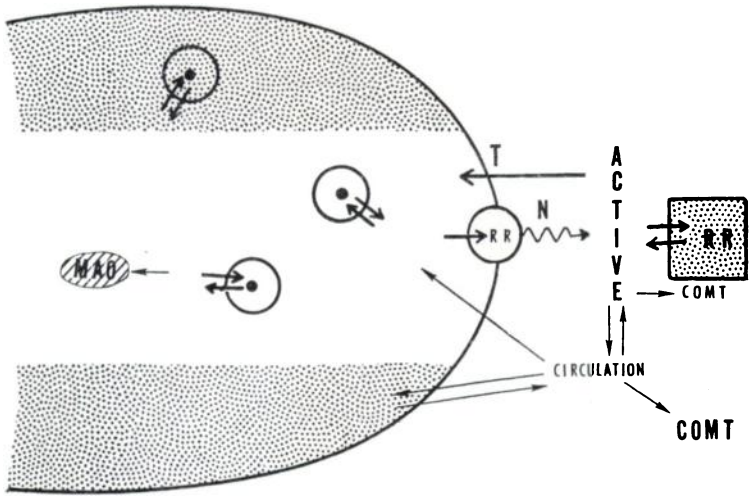

FIG. 1. Diagrammatic representation of the hypothesis relating the various storage sites of norepinephrine to the transfer and metabolic inactivation of this catecholamine.

Stippled areas represent norepinephrine available for release by tyramine; pools labeled RR are resistant to the action of reserpine; T and thick arrows indicate active transport and N refers to nerve stimulation.

while nialamid alone has no effect (24). This may indicate that in this preparation, intracellular binding and destruction by MAO are necessary for efficient removal of norepinephrine from the area of its receptor.

IV. HYPOTHESIS RELATING TISSUE STORES OF NOREPINEPHRINE TO INACTIVATION AND METABOLISM

In order to summarize our current concepts of the relation of tissue stores of norepinephrine to the metabolism and inactivation of this neurotransmitter, a hypothesis which includes the various concepts discussed above is presented (fig. 1). Various features are freely borrowed from the presentations of the numerous investigators cited, in an attempt to present a fair description of current thinking in the field.

Norepinephrine is present mainly in vesicles in sympathetic nervous tissue. The vesicles are distributed along the axon and at the nerve endings. Norepinephrine in the vesicle is in equilibrium with unbound norepinephrine in the cell fluids which is available for destruction by MAO, and to some extent for diffusion out of the cell. There is an active transport mechanism or transfer site (T) which maintains a higher concentration of norepinephrine in the cell than in the extracellular fluid. Sympathomimetic amines can release (probably by replacement) only a portion (shaded) of the particle-bound norepinephrine and they also interfere with the transport. Reserpine decreases the binding capacity of the vesicles, allowing the stored norepinephrine to have access to the MAO.

While reserpine can deplete most of the norepinephrine in tissue, there appear to be two small pools which are resistant to the action of this drug. One of these

pools (RR, unstippled) serves as a source of norepinephrine release by nerve stimulation (N). This pool appears to be resistant to tyramine, so that nerve stimulation can still evoke a response after the development of tachyphylaxis to a sympathomimetic amine. Some have speculated that this pool is in the nerve membrane (48, 80). It may normally be replenished by norepinephrine from the intraneuronal vesicles, and may in fact be made up of vesicles which have been incorporated into the membrane. This pool is, of course, depleted by reserpine if the sympathetic nerves are intact. An extraneuronal pool, resistant to the action of reserpine but released by the action of tyramine, becomes apparent after chronic sympathetic denervation (RR, stippled).

Norepinephrine released by nerve stimulation is mainly transported back into the nerve, where binding into the vesicles, competing with MAO, preserves some of the intracellular norepinephrine. Smaller portions of the released norepinephrine are destroyed by COMT, or enter the circulation and are excreted, O-methylated, or rebound in another tissue.

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