THE STORAGE AND RELEASE OF CATECHOLAMINES

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One hundred and two years ago Vulpian demonstrated the presence in adrenal glands of a material which gave a green color with ferric chloride (168). He also showed that this material appeared in adrenal venous blood (168). Although he did not know it, he was probably demonstrating for the first time the storage and release of catecholamines. Subsequently, tissues which accumulate catecholamines have become known as chromaffin tissues (113) because of their ability to show a characteristic histologic staining reaction due to the reduction of chromates (80). The presence in adrenal medulla of pharmacologically active material (134, 163) and its release under conditions of stress (163) were well known before the end of the last century even though the chemical constitution of adrenaline was not established for another five years (36, 160). Only in the last 20 years have significant quantities of a second catecholamine, noradrenaline, been demonstrated in adrenal medulla (7, 69, 96, 98, 101) and sympathetic nervous tissue (51). Although for a long time it had been argued that the material liberated from sympathetic nerve endings was not adrenaline but some chemically related compound (30) and although some shrewd speculation as to the nature of this transmitter material had been made (75, 130, 159), only recently has it been established that the material liberated from sympathetic nerve endings is in fact noradrenaline (141). A third amine, dopamine (dihydroxyphenylethylamine), has also been identified in adrenal medulla (71, 155) and it has now been shown to constitute a large proportion of the catecholamine of sympathetic nerve fibers (56, 72, 149, 151, 152).

Significant amounts of catecholamines have been found in certain insect and plant tissues. Thus dopamine, noradrenaline and adrenaline have all been detected in bees and meal worms (136). Dopamine has been isolated from broom (147) and in the past year both dopamine and noradrenaline have been found in bananas (169). Adrenaline is also present in the parotid glands of the toad (1).

The presence in mammalian tissues of three catecholamines, adrenaline, noradrenaline and dopamine has been established. The cells in which these compounds are found are principally the cells of the sympathetic nervous system, including the related chromaffin tissue. The precursors of these tissues are derived from the neural crest of the embryo as primordial sympathetic ganglion cells; only after migrating outside the central nervous system do some of the ganglion cells become further differentiated as adrenal medulla cells (35, 66, 113, 129) and to a lesser extent as paraganglia (including the organs of Zuckerkandl). Very little is known about paraganglia; they give a characteristic chromaffin reaction (114) and they contain catecholamines (154), in some cases (organs of Zuckerkandl) certainly noradrenaline and adrenaline (173). No knowledge is available concerning the storage of catecholamines in paraganglia or of their release therefrom; it is generally inferred that they function as accessory adrenal medullae, and in man some of them degenerate during the first 3 years of life (35, 173). Outside the sympathetic nerves and chromaffin tissue all three catecholamines are found in the central nervous system (34, 131, 167) but as this subject will be discussed elsewhere in the symposium it need not be considered here. Catecholamines have also been reported in other mammalian organs such as the spleen (50, 55, 58), lungs (56, 152), heart (52, 100) and blood vessels (57, 148). There is no evidence that the catecholamines are outside the sympathetic nervous tissue of these organs and until evidence for a non-nervous location is forthcoming it is probably safe to assume that the amines are within sympathetic nervous structures. Of course this cannot be so in the case of blood. The subject of blood catecholamines is being discussed elsewhere in this symposium. Attention might be drawn to the presence of small amounts of noradrenaline in platelets (15, 170) (approximately 0.006 $m\mu g/10^8$ platelets). This is presumably catecholamine which has been taken up from the plasma; there is evidence that platelets also have the ability to take up another simple amine, 5-hydroxytryptamine (78).

Contrary to earlier views that the catecholamines of sympathetic nerves consist of a mixture of adrenaline and noradrenaline, this mixture being sometimes referred to as sympathin (30, 51), recent careful analyses indicate that the catecholamines of sympathetic nerve cells are almost exclusively dopamine and noradrenaline (53, 57, 149, 151, 152). Sympathetic nerves and sympathetic ganglia contain only a few micrograms of catecholamine per gram of tissue (151); about half of this is noradrenaline and the remainder is principally dopamine (147, 151). The concentration of noradrenaline is higher in the terminal parts of the nerve fibers than in the more proximinal nerve trunks (53). The presence of the relatively large amounts of dopamine suggests that it is being synthesized more rapidly than it can be oxidized by any amine oxidase in the nerve fiber or that the dopamine is so located that it does not come into contact with amine oxidase. All three catecholamines, adrenaline, noradrenaline and dopamine, have been found in adrenal medulla (101, 125, 153, 155, 171, 172); the relative amounts of each vary according to species. Dopamine is present usually only in traces, but a relatively high value, namely 2% of the total catecholamine content, has been reported in the adrenal medulla of sheep (38). It is rather surprising that so much dopamine should be present in medulla because, lacking the β-hydroxyl function, it is, unlike adrenaline and noradrenaline, an excellent substrate for amine oxidase (9), and adrenal medulla does possess an active amine oxidase (120). The principal catecholamines of adrenal medulla, adrenaline and noradrenaline, are usually present in amounts of 5 to 10 mg per gram of tissue (13, 33, 83). In the adrenal glands of adult primates there is very little noradrenaline (172), whereas in birds and amphibia half or more of the adrenal catecholamine may be noradrenaline (103, 153, 171). Rather full tables of the relative proportions of these two amines in the adrenal medullae of different species are available (73).

There is good evidence that in some mammals including man noradrenaline is the predominant adrenal catecholamine in fetal and neonatal life (153), the proportion of adrenaline stored in the adrenal medulla increasing as the animal becomes older (172). Recently the opposite has been observed in a group of chickens; two were killed at birth and their adrenal glands contained only adrenaline; two were killed in each of following months. The proportion of noradrenaline rose until at 6 months about 30% of the adrenal catecholamine was noradrenaline (76). It is remarkable that the adult chicken, which has a higher proportion of noradrenaline than primates, can begin life having only adrenaline in its adrenal glands whereas a primate, which in the adult stage has mostly adrenaline, can begin life having mainly noradrenaline.

The recent development of new techniques in histochemistry, in the electron microscopy of ultrathin sections and in the centrifugation of cell particulate materials has facilitated investigations of the cellular storage of catecholamines.

There has been much discussion concerning the possible presence in the adrenal medulla of separate adrenaline-storing and noradrenaline-storing cells (6, 49, 86–89). Adrenal medulla cells are ontogenically sympathetic nerve cells (114, 129) which have been modified so that they liberate their secretion directly at the surface of the cell body and thence into the circulation instead of at the distal end of an axon in the vicinity of the effector organ. They differ also in having the capacity to methylate noradrenaline to adrenaline (20, 112). It might be possible that some of the cells have remained more like sympathetic nerve cells in lacking a methylating system. This, however, is merely speculation. The evidence for separate adrenaline-storing and noradrenaline-storing cells rests principally on differential staining reactions (6) or differential fluorescence (49) of different areas in thin sections of adrenal medulla. Thus, staining with Giemsa stain (6) or potassium iodate (86–89) suggests the presence of two types of cell, as do descriptions of differently fluorescing cell groups (49). Perhaps we should be hesitant in accepting that these differences are due solely to the differences in the adrenaline and noradrenaline contents of the different areas of the medulla if we remember that potassium iodate reacts with both adrenaline and noradrenaline to give dark pigments. Furthermore the histochemical technique depends on subtle differences in the rates of oxidation of the two amines or on the effect of pH on the relative rates of the reactions. From the biological viewpoint a disturbing feature with the fluorescence technique is the claim, advanced to support the validity of the method, that the injection of nicotine into the animal before removal of the adrenal glands causes the disappearance of the fluorescence in the noradrenaline areas without affecting that in the adrenaline regions (49). This argument implies that some of the cells are sensitive to nicotine and others not, a supposition for which there is so far no evidence. Definite proof of the existence of separate adrenaline- and noradrenaline-storing cells will probably have to await the development of histochemical techniques specific for the N-methyl function. It might be possible to label the adrenaline *in vivo* with methyl C^{14} or tritium-labeled methionine as the methyl donor and subsequently to make autoradiographs of stained sections of the medulla with stripping film.

We are on more secure ground in discussing the intracellular storage of catecholamines in adrenal medulla. Since the demonstration by Blaschko and Welch

(14) that in this gland the catecholamines are largely held within intracellular particles much information has become available concerning the nature of the particles. Because the granules were first isolated by differential centrifugation together with mitochondria it was thought by some workers that they might represent specialized cell organelles related to mitochondria (92). However, evidence gradually became available suggesting that the catecholamines are stored in granules other than mitochondria (11, 43a). Recently, by centrifugation of the large granules in a specific gravity gradient it has been possible to obtain two different types of granule (12); on electron microscopy the less dense granules, which remain near the top of the gradient, show the characteristic morphology of mitochondria (5); they contain such typical mitochondrial enzymes as fumarase, succinic dehydrogenase and amine oxidase, but insignificant amounts of catecholamine (12). The denser granules, which settle to the bottom of the gradient, contain very large amounts of catecholamines and ATP and lack the enzymes reported in adrenal mitochondria (12). On electron microscopy they appear quite unlike mitochondria (5). Excellent electron photomicrographs of adrenal medulla have been available in the last few years (123, 145, 174). They show two distinct types of large cytoplasmic inclusions: relatively sparse, typical mitochondria and more numerous, smaller dense round bodies structurally identical with the large isolated granules containing the catecholamines (123, 145, 174). The dense catecholamine-containing granules have been called "chromaffin granules" by Blaschko (10) and "pheochrome granules" by Wetzstein (174).

In electron photomicrographs chromaffin granules are approximately circular in outline and are of varying sizes (145, 174). Their diameter is usually between 50 and 90 mμ (174). They are thus smaller than mitochondria and very much smaller than another amine-storing granule, namely the histamine-bearing granules of mast cells, which are considerably larger than mitochondria (77). The chromaffin granules are more numerous than mitochondria and in ox medulla may be so numerous as to almost completely obscure the presence of other intracellular organelles (5). They appear to occupy "spaces" in the endoplasmic reticulum of the cell and are distributed through the cytoplasm in smaller or larger groups (174). The granules have a finely stippled internal structure and an outer membrane which is thinner and less conspicuous than a mitochondrial membrane (174).

Chromaffin granules are stable in isotonic solutions but release their amines (13), their ATP (84) and about 77% of their protein (82, 83) into the suspending medium when placed in hypotonic solutions. The intravenous injection of a suspension of these granules in an istonic medium exerts only about one-fifth of the immediate effect on blood pressure of the cat that would be expected on the basis of its catecholamine content. However, when the granules are first lysed in distilled water the full effect of the catecholamines is seen immediately on injection (13). The granules can be made to release their amines not only by changes in the tonicity of the medium but also by treatment with certain detergents or histamine-liberators, and by changes in the pH of the suspending solution, but not by the addition of carbachol, acetylcholine or histamine, any of which causes the release of catecholamine from the adrenal medulla *in vivo* (13, 43, 91).

Several years ago it was noticed that adrenal medulla contains more ATP (adenosinetriphosphate) than other mammalian tissues, about 5 mg per gram of tissue (85), and that this ATP is in the large granule fraction (59, 85). We know now that it is almost entirely held within the chromaffin granules (12), where the molar ratio of amines to ATP is approximately 4:1 (33, 39). Thus it seems that ATP serves as the anion paired with the basic catecholamines. Determinations of the catecholamine content of the granules indicate that at least 15 to 20% of the dry weight of the particles is catecholamine (13, 42); about another 15% must be ATP. Neglecting any other constituents of the chromaffin granules [the only other constituents we know of are water (13), protein (13, 92), and cytochrome-m (158)], ATP and catecholamine alone would constitute quite a highly hypertonic solution in the granule if present as free ions in solution. On the other hand it is possible to imagine the ions of both these compounds held in some way to protein at the cyclic ends of their molecules, in each case so that they are not free ion particles in solution but held in such a way that the unattached anionic and cationic tails of the ATP and catecholamines neutralize each other's charges.

Cytochrome-m is a cytochrome characteristic of microsomes and not present in mitochondria (161). Its presence in chromaffin granules (158) indicates that they are probably derived from the endoplasmic reticulum of the adrenal medulla cell. This suggestion is not without parallel elsewhere in view of evidence for a derivation of secretory material from endoplasmic reticulum in pancreas (156).

At present we do not know whether the chromaffin granules are solely storage granules or whether some of the reactions involved in the biosynthesis of adrenaline and noradrenaline also occur there. This question will undoubtedly have received attention in the papers on biosynthesis. It is known that in other tissues phosphorylation reactions involved in the formation of ATP take place in mitochondria (68, 157). The presence of respiratory enzymes in adrenal mitochondria (12) suggests that this is also the case in this tissue. The absence of tricarboxylic acid cycle enzymes from the chromaffin granules (12) suggests that the ATP which they store is made elsewhere. That methylation of noradrenaline to adrenaline takes place outside the granules (112) suggests that the adrenaline enters the granules only after it is synthesized. It is known that the hydroxylation of dopamine to noradrenaline is a function of the unseparated large granule fraction of adrenal medulla (112), but whether the mitochondria or the chromaffin granules are the responsible particles is so far undetermined. It is tempting to speculate that the hydroxylation takes place in or on the mitochondria and that the formed noradrenaline, paired with an equivalent amount of ATP, then enters the chromaffin granule, some or all becoming methylated to adrenaline in transit from the one organelle to the other.

In homogenates of chicken adrenal gland a small fraction of chromaffin granules has been isolated which contains only adrenaline while another small fraction contains only noradrenaline (150). However, the majority of the granule-fractions has contained a mixture of both amines (150). This may mean that the technical difficulties of separating all the granules into the adrenaline type and the noradrenaline type were too great or it may indicate that the majority of granules does contain a mixture of the two amines. While the presence of two types of granule could fit in with the idea that there are separate noradrenaline-containing cells and adrenaline-containing cells, there is no reason why separate adrenaline granules and noradrenaline granules might not exist in the same cell. Anatomists have described changes in shape, location and composition of the chromaffin granules during secretion (145). De Robertis and Vaz Ferreira have made electron photomicrographs of the adrenal medulla of rabbits both before and after strong stimulation of the splanchnic nerve (145). They observed a reduction in the denseness of the chromaffin granules and in some cases changes in the relation of the granules to the cell membrane, to which they became attached. The natural history of the chromaffin granules might be that they begin as small vesicles derived from the endoplasmic reticulum, gather catecholamines and ATP, increase in size, and finally excrete their contents at the cell surface. In this case ATP should be extruded with the catecholamines, which in fact is in agreement with findings that in rats, cats and sheep the ATP level falls (31). Despite careful analyses it has been impossible to find the products of the splitting of ATP in the cytoplasm of the gland either inside or outside the granules (31). On the other hand it has also been reported that in rabbits the amines may be secreted with very little loss of ATP (39). Further experiments are obviously needed. The noradrenaline of sympathetic nerve fibers is also contained within granules with sedimentation characteristics similar to those of the chromaffin granules of adrenal medulla (53, 151). As already mentioned the catecholamines in sympathetic nerves consist of dopamine and noradrenaline; the dopamine is found principally in the non-particulate cytoplasm whereas a large part of the noradrenaline is located in the granules (151); thus there is a difference from adrenal medulla where the dopamine is largely intragranular (43b). Nothing is known concerning any morphological changes occurring during the release of catecholamine at sympathetic nerve endings.

Studies with adrenaline labeled *in vivo* by the previous injection of C^{14} tyrosine or phenylalanine have shown that radioactive adrenaline may be found in the adrenal gland for many days after its synthesis (165), thus indicating a long storage time. Experiments in which the adrenal glands have been depleted of their amines either by insulin-induced hypoglycemia or by the repeated injection of acetylcholine have indicated that about two weeks elapse before the catecholamines in the gland are restored to their usual level (25, 26, 165). Both these observations have been interpreted as indicating that in adrenal medulla adrenaline is very slowly synthesized and only slowly released; that is, that the turnover rate of adrenaline is slow (165). Likewise, in experiments in which radioactive dopamine has been incubated with homogenates of adrenal medulla the formation of radioactive noradrenaline has also been slow (77a). However, some acute experiments have shown that replacement may be fairly rapid (137) and that in certain circumstances the sum of the amounts of catecholamines secreted and recovered in the gland at the end of the experiments has exceeded the amounts originally present in the gland (94). Perhaps these apparently contradictory findings can be reconciled by assuming that the rates of synthesis and secretion of newly formed amine may be relatively rapid whereas the building up of stores and the release of stored amine might be relatively slow processes (165).

Although the adrenal medulla can secrete both adrenaline and noradrenaline (17, 21, 55, 67, 99, 107, 128, 137, 166) it seems that adrenergic neurones release principally if not only noradrenaline (126, 127, 138, 139). Although in addition to noradrenaline, dopamine is also found in sympathetic nerves (149) there is no evidence for its release; in fact, there is no record that the possibility of its release has been investigated. It is possible that the dopamine in sympathetic nerves serves solely as precursor (74) material for an unlimited supply of noradrenaline. However, the possibility must be considered that dopamine may be liberated and may have a function in its own right.

As previously mentioned, chromaffin cells of the adrenal medulla and sympathetic nerve cells are derived from the same undifferentiated precursor cells (114, 129); thus analogous preganglionic cholinergic nerve fibers supply both (63, 46, 95). In other words the synapse between the preganglionic nerve ending and postganglionic sympathetic nerve soma is to the best of our knowledge similar to if not identical with the synapse between the preganglionic fiber and the chromaffin cell of the adrenal medulla (46, 63). Similarities and differences between the actions of pharmacological agents at these sites have been reviewed by other workers (118). Acetylcholine (61, 62, 70), carbamylcholine (60), choline (64, 70), nicotine (27, 37, 46, 64, 106, 107), lobeline (105, 106, 115), potassium chloride (47, 64, 110, 137), pilocarpine (2, 37), tetramethylammonium (44, 118), histamine (24, 111, 116, 162), morphine (45, 46, 79, 104,) veratrum alkaloids (117, 119) and serotonin (122, 144, 146, 164) all cause the release of catecholamines from both sympathetic nerve fibers and adrenal medulla cells. There are, however, certain differences in the response of sympathetic nerve cells and adrenal medulla cells to pharmacologic agents. Thus cyanide or anoxia (22) can cause the release of catecholamines from adrenal medulla but not from sympathetic nerves (117). Antihistamines likewise stimulate the release of catecholamines from adrenal medulla (47) but depress the excitability of sympathetic ganglion cells to acetylcholine (42). Intensive stimulation of the nerves to the adrenal medulla or of preganglionic sympathetic nerves appears to cause a relatively slight depletion of the catecholamines present in the gland or nerve. Prolonged, repeated, intensive stimulation seems to be necessary before any marked depletion can be brought about (25, 81, 108, 135).

In recent years it has been observed that reserpine can cause the disappearance of catecholamines from adrenal glands (32, 102), sympathetic nerves (133), heart (8, 140) and brain (102). This apparently is due to a release of the amines from chromaffin tissue rather than to an inhibition of their synthesis (118a, 132, 140). The mechanism of this release is quite mysterious. Removal of noradrenaline from the sympathetic nerve fiber may be so complete as to interfere with transmission between the nerve ending and the effector organ (34a, 133). Thus, in an experimental animal treated with reserpine, stimulation of the accelerans nerve fails to evoke cardioacceleration (164a) and stimulation of the cervical sympathetic trunk either proximal or distal to the superior cervical ganglion fails to cause contraction of the nictitating membrane (133). Iproniazid can largely prevent this depletion (97) and the mechanism of this action of iproniazid is equally mysterious; there is no evidence that it is mediated by the ability of iproniazid to inhibit amine oxidase.

Stresses such as anoxia (163) and sudden excitement (27a, 28, 45) are known to cause the liberation of catecholamines from adrenal medulla and sympathetic nerves. These are examples of centrally arising or reflex stimuli, which pass down the spinal cord and across the cholinergic preganglionic fibers to the adrenal medulla and sympathetic nerve cells alike. At present little is known about the central stimuli responsible for the peripheral release of catecholamines but some information is available. The effect of hypoglycemia for example is directly on the hypothalamus (41) to initiate impulses causing a discharge of adrenal catecholamines (29). Electrical stimulation of parts of the hypothalamus (16, 18, 19, 67) or of areas of the cerebral cortex (65) known to influence autonomic activity can cause the liberation of catecholamines into the adrenal venous blood. Whether there is a selective secretion of adrenaline or noradrenaline from the adrenal medulla according to the nature of the central stimulus is a matter on which different workers hold divergent views. The evidence for selective secretion is based largely on bioassay of mixtures of adrenaline and noradrenaline in adrenal venous blood (17, 18, 19, 54, 55, 67, 109). It is also based to some extent on the observed effects on peripheral organs of the experimental animal when its adrenal medulla is activated by different stimuli (142). It seems that the estimation of very small quantities of adrenaline and noradrenaline when both are present should be preceded by a separation of the two amines either by paper or column chromatography, if one is to be certain of the relative proportions of the two compounds, irrespective of the bioassay procedure. Studies in which the precaution has been taken to separate the amines before their estimation, as well as some studies in which this precaution has not been taken, have failed to show a selective secretion (25, 40, 107, 128, 166). Indeed there is evidence that the proportions of adrenaline and noradrenaline in adrenal venous blood are the same as the proportions found in the gland (25, 166). Only further, carefully controlled experiments can settle this question.

Denervation of the sympathetic nerve cells or adrenal medulla by cutting the preganglionic fibers does not seem to impair the ability of these cells to store catecholamines (93, 143, 166). Section of the postganglionic fibers can cause the loss of noradrenaline from the peripheral fibers. It is replaced as the fibers regenerate (143). Stimulation of decentralized sympathetic nerve fibers causes the usual liberation of noradrenaline at the effector organ (18a). Likewise, stimulation of the denervated adrenal medulla cells, *e.g.*, by the injection of potassium chloride into the adrenal blood supply (166) seems to provoke the expected secretion of catecholamines.

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