Pathophysiological Aspects of Catecholamine Production

U. S. von Euler

The production and function of catecholamines and their variation during various normal and abnormal conditions are discussed.

Additional Keyphrases: urinary vanillylmandelic acid - effects of stresses, exercise, cold exposure, drugs, toxic substances, inhibitors - neural control of production - functions of catecholamines

Estimation of Catecholamines

Under normal conditions catecholamines (CA) are continuously produced and released in the organism, and play important roles in homeostatic and other functions. Of the three normally occurring CA — epinephrine (E), norepinephrine (NE), and dopamine (DA) — E is produced by the adrenal medulla and by other chromaffin cells distributed in almost every organ, while NE is mainly produced by the adrenergic neurons, and usually to a minor extent by the adrenal medulla. The production and release of DA is less well known, but there is good evidence that it occurs in the adrenal medulla, in the heart, and in the carotid body, apparently in specific DA cells (1).

While CA secretion can be directly measured from the adrenal medulla by sampling the blood from the adrenal vein, even in the unanesthetized animal, and sometimes by catheterization in man, the measurement of NE release from adrenergic nerves is more complicated. Several methods have been used. In the present context I shall confine myself to the overall production of CA in the organism and their variation in various physiological and pathophysiological conditions in man.

The estimation of free CA in urine has provided a useful method for obtaining a relative measure of the production over a given time period (2). The free amines excreted in urine constitute only a few percent of the amount delivered intravenously, but this proportion seems to be fairly constant. It has been suggested that the principal metabolite, VMA, which is excreted in approximately 100 times greater amounts, should be used instead of the free amines. Although VMA estimation should give a more quantitative measure of the catecholamine production, it does not differentiate between adrenaline and noradrenaline, which from a physiological and clinical point of view represents valuable information. It has also been noticed that while excretion of free amines varies with the functional state of the organism with relatively brief time lag, the VMA excretion does not reflect briefer variations to the same extent. Under certain conditions, measurement of other metabolites, such as metanephrine and normetanephrine, may give additional information (3, 4).

The 24-hour excretion of free CA in urine is generally about 30–70 µg, of which about 20% is E and the rest NE. About 300 µg of DA is also excreted daily (5). Because circulating DA is readily oxidized to DOPAC most of the DA is believed to be released by the kidney. The VMA excretion in urine is normally 3–7 mg per 24 hours.

Estimation of CA in blood requires arterial catheterization, because the amount of it in venous blood may be influenced by local changes in the perfused area and thus does not represent overall production.

Conditions Accompanied by Increased Excretion of E and NE

Physiological conditions. Under normal conditions, very little E is excreted during the night, about 2 ng/min; this increases to about 5–10 ng/min during the daytime hours. Increased adrenomedullary secretion has been observed in early experiments on cats...
and dogs during physical and mental stress and during hypoglycemia. Differential analysis of E and NE excretion in urine later demonstrated that E predominated, except during exercise.

Since the first studies on CA excretion in urine during stress a large number of investigations on this subject have been made. During mental stress, examinations, pain, noise, apprehension-provoking situations, exciting films, etc., the excretion of E in urine is increased (6). The excretion of NE may also be increased in certain cases (7). E excretion is increased two- to threefold, depending on the degree of stress. This in its turn may vary for a given situation, depending on the reactivity of the subject.

While light or moderate exercise generally is not accompanied by increased excretion of E, strenuous work causes augmented output of this amine.

The increased output of E in adrenal venous blood during insulin hypoglycemia illustrates the homeostatic mechanism by which glycogen breakdown is automatically induced. Another homeostatic mechanism accompanied by increased output of E is temperature regulation during cold, which has been mainly studied in animals (10).

Increased NE excretion in urine is observed in a number of conditions, which, however, are clearly distinct from those that are accompanied with increased output of E. In many cases increased secretion of NE is associated with homeostatic mechanisms involving blood pressure. An example is the increased excretion during erect position. When posture is changed from recumbent to head-up position, as studied on the tilting table, NE excretion augments up to fourfold, indicating increased activity of the adrenergic system (8). This effect is annulled by ganglionic blockers, and it is well known that such treatment may cause symptoms of orthostatism.

A reflexly induced increase in NE output of the same general kind is seen during muscular exercise. Even moderate work increases urinary NE excretion, and at maximal work the excretion may be increased by 20-fold or from 20 ng/min to 400 ng/min (9). In the case of muscular work, ganglionic blockers also cause signs of circulatory insufficiency, which may cause dizziness in patients, even at a moderate work load. Obviously the vasodilatation in the musculature is partly compensated by vasoconstriction in other areas under normal conditions.

During exposure of rats to low temperature, a large increase in the NE output has been observed (10), which remains almost unchanged during even prolonged exposure to cold. Apart from the vasoconstriction in the skin, which aids in preventing heat loss, the increased NE production mobilizes fat and enhances metabolism.

Pathophysiological conditions. All of the situations mentioned may be termed physiological, and are clearly correlated with increased demand for E or NE activity for circulatory, metabolic, or other purposes, and also for maintaining mental alertness. In the following some examples of pathophysiological conditions will be given, conducive to increased or reduced output of catecholamines.

In many pathological or pathophysiological conditions there is a less clear differentiation between E and NE excretion. In some cases the hypothalamic centers become generally activated; for example, during asphyxia and by toxins. Increased secretion of both E and NE is then often observed. After trauma and extensive surgery both amines may be excreted in increased amounts. Of special interest is the sometimes strongly increased catecholamine excretion after burns. This increase generally involves both E and NE, and appears to be to some extent correlated with the heat-loss and increased metabolism in these cases (11).

Increased NE secretion is sometimes associated with hypertension, particularly in elderly patients, without any evidence for a NE secreting tumor. In these cases it appears possible that the conditions are due to arteriosclerotic changes in the hypothalamic area. Electroshock and pneumoencephalon are often associated with increased CA output.

A number of drugs and toxic substances are also known to induce increased secretion of CA. Bacterial toxins may thus produce increased adrenomedullary secretion. Nicotine stimulates secretion of both E and NE. A slight increase is also noticed after ethanol. One of the most active toxic substances leading to increased CA excretion is thallium (12).

Various so-called autonomic drugs, in addition to nicotine, also caused increased secretion of CA. Thus, certain adrenergic blockers such as phenoxybenzamine increase the release of NE. This effect has been interpreted partly as a blockade of NE re-uptake, but may also be due to a blockade of the inhibitory effect of prostaglandins of the E type on the transmitter release (13). Cocaine also increases NE excretion, presumably by inhibiting re-uptake in the nerve endings (14). This may be true also for other re-uptake inhibitors—for instance amitriptyline and nortriptyline—and also some indirectly acting amines. Some metabolic inhibitors, such as dinitrophenol, are also known to release NE from storage particles and may in this way cause increased secretion (15).

Another mechanism for increased NE secretion is by inhibiting breakdown. This is the case for mono-amine oxidase inhibitors.

Although increased CA secretion in various conditions is far more common than reduced secretion, the latter may also occur. The clinically most important condition is postural hypotension, which may be diagnosed by the low NE output (16). The condition is apparently due to a faulty development of the adrenergic nervous system.

Decreased NE secretion can also be caused by drugs affecting synthesis, storage, and release of the adrenergic neurotransmitter. Synthesis inhibitors acting on any of the important synthetic steps—the reactions catalyzed by tyrosine hydroxylase, dopa-
decarboxylase, or dopamine-β-hydroxylase—may all cause decreased CA output, although urinary output of CA has been relatively little studied. However, the dopa decarboxylase inhibitor, "decarborane(14)" (B_{10}H_{14}), markedly decreases the CA output in urine. As a check of the efficiency of the treatment regarding the production of CA, urine analysis represents a simple, and for many purposes useful, method. In the case of treatment with α-methyl-dopa, analysis should include α-methyl-noradrenaline, which is biologically highly active.

Of other drugs special mention should be made of reserpine and drugs having a similar action. These drugs prevent the uptake of the newly synthesized NE into the storage particles in the nerves (17), and in addition inhibit the release of the amines from the particles. After therapeutic doses in man, reserpine therefore causes a marked decrease in the output of NE. Reserpine treatment can thus be monitored by urine analysis. The same holds true for ganglionic and neuronal blockers such as bretylium or guanethidine. Clinical monitoring of these effects can be routinely made by mechanized CA analysis of urine samples. It would be of interest systematically to compare the clinical effects and the effect on CA output in urine of the various drugs affecting CA metabolism.

Neural Control of CA Production

Production. CA production, both in the adrenal medulla and in the adrenergic nerves, is controlled by nerve impulses that are to a large extent mediated through relay stations in the hypothalamus. It has been shown that the adrenomedullary secretion is not only differentiated with regard to E and NE, but also that it can be inhibited from certain areas in the forebrain (18). Various stimuli, perhaps in the first place psychic, can thus lead to increased or decreased secretion of either E or NE.

The adrenergic system, which to a large extent subserves the regulation of the width of the vascular bed and determines the degree of vasoconstriction in different areas, has its reflex synapses mainly in the medulla oblongata or in the spinal cord, but receives input signals from various areas in the brain. In this way a certain differentiation of vasoconstriction to certain areas can be achieved.

Effects. Although E and NE have a number of actions in common, important functional differences exist. Perhaps the most characteristic differences are the psychic effects of E, which do not occur with NE (19). The action pattern of E in this respect was clearly recognized by W. B. Cannon, who very aptly termed adrenaline an emergency hormone, being secreted in conditions of anger and fright, and apparently sustaining and reinforcing these emotions, thus preparing for life-saving actions such as fighting or fleeing. In cases where adrenalectomy has been performed for therapeutic reasons and the cortical functions upheld by substitution therapy, the loss of adrenomedullary secretion seems to alter the behavioral pattern in the patients toward a state of complacency. A moderate increase in E secretion, as seen for example after cigarette smoking, has been shown to improve mental efficiency (20), and a beneficial effect on learning has been observed in rats receiving small doses of nicotine (21).

Taking all the actions of E together, it may be stated that this amine stimulates a number of functions of importance for the relationships of the organism with the ambient world, be it aggression, defense, or mental alertness. NE, on the other hand, is indispensable for the autonomic homeostasis, maintenance of blood pressure, and temperature, sometimes at the cost of other functions such as digestion, and has important actions on fat mobilization. If E may be said to have executive functions in the department of foreign affairs, NE plays a similar role in internal affairs, looking after the day-to-day activities.

From these activity patterns it is also easy to see what may happen in cases of hyper- or hypoactivity, alone or combined, of these two key hormones for external and internal activity. They need not be further specified here, but, because a large number of conditions may be accompanied by hyper- or hyposecretion of these amines, it is clearly of interest to obtain information as to whether this occurs. In cases of hypertension a measurement of NE output is particularly useful, because the occurrence of an amine-producing tumor can be diagnosed in this way (22).

Interactions. Interactions between the CA and other hormones have been observed in increasing number. Because many of these are assumed to take place at the receptor areas on the cell surface, they form part of the increasingly studied subject, molecular pharmacology. This branch of macromolecular chemistry still awaits a breakthrough, but there is a reasonable hope that receptor macromolecules will eventually be isolated, perhaps with the aid of specific agonists or blockers forming suitable complexes.

Of special interest in this context is the activation by CA of adenyl cyclase, leading to the formation of cyclic AMP (23). This effect is so far the best example of an interaction between CA and macromolecules of the reacting cell membrane. It has recently been observed that not only E and NE but also DA activates this process, as shown for the superior cervical ganglion (24). The local accumulation of DA in certain areas, such as in the carotid body and in the sinus node in the heart, may in this way find an explanation.

Inhibition of adrenergic activity may also be associated with structural changes such as those observed with 6-hydroxydopamine (25) and guanethidine (26), which may cause long lasting damage to some cell structures that are of importance for adrenergic nerve function. Thus 6-hydroxydopamine destroys the adrenergic nerve endings and the axonal microtubules by which some of the macromolecules necessary for NE synthesis are presumably trans-
ported from the cell soma. Guanethidine, on the other hand, causes deterioration of the organelles in the adrenergic nerve terminals, and in this way prevents synthesis and release. A damaging effect on mitochondria has also been described for reserpine.

The last-mentioned examples illustrate that the action of drugs used to modify the amine secretion may do so not only by functional interaction with the normal processes, but also by gross disturbances of their structural basis.

Part of the studies on which this review is based were supported by Swedish Medical Research Council Grant No. B73-04X-3186-03A.

References


