III. EPINEPHRINE AND NOREPINEPHRINE

ADRENALINE AND NORADRENALINE. DISTRIBUTION AND ACTION

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Important knowledge about the nature of the chemical substances released from postganglionic nerve endings has been gained by studies of their occurrence in tissues and organs. In this way it has been demonstrated that the specific active substance of adrenergic nerves is noradrenaline, identified by biological assay of the active principle concomitantly with chemical tests (6, 7). (For a more detailed historical account, see 9, 10.)

The results of studies on the release of adrenergic nerve transmitter substances in vivo (4, 23, 26, 31, 47, 51) have all given support to the conclusion that the specific sympathetic mediator is noradrenaline.

Occurrence and distribution. The amount of noradrenaline varies greatly in different organs but can be correlated to the extent of the sympathetic nerve supply to an organ (9, 10, 30; 37). Accordingly the spleen is comparatively rich in noradrenaline, while on the other hand the lung and striated muscle contain small amounts. In the nerve-free placenta no catechol amines are present. The noradrenaline content in various peripheral nerves also varies with the amount of post-ganglionic sympathetic nerve fibres in the nerve trunk.

The relatively high content of noradrenaline in an organ such as the spleen obviously cannot be explained by the content in the periarterial nerve trunks—up to 18.5 μg per g—if they contain the same amount per g throughout their entire length.

Slightly increased figures for noradrenaline in the peripheral nerve branches of the cow's spleen have been observed. However, if splenic nervous tissue is estimated as less than 0.5 per cent of the whole organ weight, the amount of noradrenaline would be less than 0.1 μg per g of whole spleen, even using a mean figure as high as 20 μg noradrenaline per g nerve. The figure 0.1 μg per g, however, is much lower than that actually found which is 3 μg per g of spleen. This strongly suggests that the concentration of noradrenaline in the nerve endings is far higher than that in the nerve trunk itself. If the weight of the nerve endings, which are actually engaged in the release of noradrenaline, is estimated to represent between 1:1,000 and 1:10,000 part of the spleen, one would arrive at approximate concentration figures of between 3 and 30 mg per g of such terminal structures. These figures, moreover, are in the same range of concentration of catechol amines as those found in the suprarenal medullary cells.

We do not know in which state the catechol amines are present in the nerve endings, but recent independent investigations (2, 33) have indicated that in

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chromaffin cells the catechol amines occur enclosed in microspheres which can be isolated from the cell bodies (presecretory granules). The active substances can be released from these microglobules by various procedures interfering with the integrity of their membrane. The high concentration in the adrenergic nerve terminals might be explained by assuming some similar kind of storage. The noradrenaline content in the nerve trunk itself and in the sympathetic ganglia may be physiologically insignificant and merely a biochemical artefact, since the synthesizing enzymatic system, probably originating from the cell soma, may occur, to some extent at least, outside the nerve terminals.

The postulated sudden appearance of large concentrations of the transmitter substance in the nerve terminals would seem difficult to imagine if the axons were structurally homogeneous. It might therefore be fruitful to look for some specific structure at the terminals. In this connection it should be mentioned that in C-fiber axons less than 1 μ in diameter Gasser (28) has demonstrated the presence of mitochondria. Similar structures may provide a clue as to the state of occurrence of the noradrenaline in the nerve terminals.

On the basis of present evidence it can be stated that every organ or tissue which receives adrenergic nerves also contains noradrenaline in a fairly constant concentration, being roughly proportional to the supply of such nerve fibres. This makes the assumption likely for a rapid replenishment of the noradrenaline in the nerve terminals after release, so that the content is practically always maximal. Experiments seem to verify this. Thus the content in the cat's spleen after stimulation of the nerves for 10 minutes, which should release a quantity about as high as the content of the whole organ, or about 4–8 μg noradrenaline in the average cat (51), was entirely within the normal limits. No consistent difference was observed between a stimulated and a non-stimulated portion. This rapid resynthesis is in marked contrast to the slow synthesis of adrenaline in the suprarenal gland (37, 54).

If the noradrenaline in the organ is derived from the adrenergic nerves its disappearance after degeneration of these fibres would be expected. This is actually the case as shown by several workers (3, 22, 30). Moreover Goodall (30) made the important observation that several weeks after sympathectomy of the sheep's heart noradrenaline began to reappear owing to regeneration of adrenergic fibres from the sympathetic trunk.

The source of adrenaline in tissues. After methods of differential assay of noradrenaline and adrenaline in organ extracts had been developed (8, 27) it was shown that almost all organs contained small amounts of adrenaline in addition to noradrenaline (10) (Table I). The source of this adrenaline has been a point of some dispute. The idea that adrenaline should be the mediator of adrenergic fibres in some animals such as the rabbit has been disproved, however, by the analyses of rabbit nerves and organs (9) and of the venous outflow from a stimulated organ (47).

It cannot yet be stated with certainty whether the small amounts of adrenaline, usually less than 10 per cent of the total adrenaline and noradrenaline present in organs and in venous blood from a stimulated organ, is derived from the

TABLE I

Noradrenaline and adrenaline content in various organs of the sheep

Organ (sheep)	Noradrenaline µg/g	Adrenaline µg/g	Adrenaline %
Spleen	3.0–3.3	0–0.11	0–3.4
Parotid gland	0.5–2.2	0.03–0.19	5–14
Submaxillary gland	0.4–1.1	0.10–0.21	12–21
Heart	0.6–1.1	0.1–0.2	10–20
Kidney	0.4–0.6	0.05–0.07	11
Liver	0.15–0.20	0.007–0.011	4–7
Lung	0.08–0.1	0.002–0.01	2.5–10
Striated muscle	0.025	0.0013	5
Brain	0.08		
Sciatic nerve	0.14		
Mesenteric nerves	3.5		
Splenic nerves	8.0		

adrenergic nerve endings themselves or from other structures, presumably chromaffin cells. There is some evidence, however, which speaks in favor of the latter assumption. After postganglionic denervation of the submaxillary gland in sheep the noradrenaline content dropped sharply to very low figures, while in several instances the adrenaline concentration fell but moderately (22). This would be consistent with the assumption that the adrenaline is derived from chromaffin cells which even after "preganglionic" denervation continue to produce their specific product.

The question whether noradrenaline is the sympathetic nerve transmitter also in non-mammals cannot yet be answered conclusively. Analyses of organs from molluscs, teleosts (12), and insects (48), have shown the presence of noradrenaline together with varying amounts of adrenaline, but a complicating factor in studies of this kind is the presence of chromaffin cell groups which may contain adrenaline and noradrenaline. In teleostian hearts and livers the relative amount of adrenaline was high, while in the posterior salivary glands of *Octopus vulgaris* (12) and in insect larvae (48) noradrenaline was predominant.

In Cannon and Rosenblueth's experiments stimulation of sympathetic nerves released enough transmitter substances to be demonstrated by remote effects, and subsequent authors have demonstrated beyond doubt that the venous effluent from organs after stimulation of their sympathetic nerves (46, 47, 51) contain noradrenaline and often some adrenaline. Whether the release of an adrenaline-like substance from frog's heart on stimulation of its sympathetic nerves as demonstrated by Loewi (41) was actually due to a transmitter substance from adrenergic fibres or to secretion from chromaffin cells is not entirely clear. It appears that the active substance has predominantly the properties of adrenaline (6, 42, 49), and since, for instance, the frog's spleen contains chiefly noradrenaline (49) the nerve transmitter for the heart would also be expected to be noradrenaline and not adrenaline. The frog's heart has no coronary vessels which in mammals are supplied with noradrenaline-producing vasomotor fibres.

Occurrence in body fluids. If noradrenaline under certain conditions is actually released from adrenergic nerves into the blood it should be theoretically possible to demonstrate it in circulating blood. This is also made likely by the occurrence of noradrenaline in urine, even after bilateral adrenalectomy which greatly diminishes the adrenaline output (15). Using his fluorimetric method, Lund (44) was unable to demonstrate noradrenaline or adrenaline in human venous blood (limit of sensitivity about 1 μg per liter), but it has recently been claimed (55) that some 1–1.5 μg adrenaline and 5 μg noradrenaline per liter of venous blood is present. More experiments are required to permit a definite judgment as to the concentration of adrenaline and noradrenaline in peripheral blood.

As already mentioned, human urine normally contains noradrenaline, presumably derived primarily from the adrenergic nerves, since the amount excreted remains largely unaltered by bilateral adrenalectomy. The figures obtained by analysis of urine after adsorption of the catechol amines on alumina and biological assay (17), depend on the physiological conditions during collection. At rest the figures are low, increasing with the degree of activity, especially if this involves increased vasomotor activity. During rest or moderate activity the output of noradrenaline is 20–60 μg per 24 hours, not corrected for the loss of about 25% during the extraction procedure. The adrenaline output is considerably smaller and usually amounts to 3–9 μg per 24 hours, falling to about 1 μg after bilateral adrenalectomy (15). Factors which increase the adrenaline secretion from the suprarenal medulla, such as insulin hypoglycemia, also increase the output in urine (20). From infusion experiments in man it has been found that about 1 per cent of the infused adrenaline (53) and 1.5–3.3 per cent of infused noradrenaline (19) are excreted per unit of time.

Sympathomimetic amines have also been extracted from milk, but none has been detected in cerebrospinal fluid or aqueous humour, although the sensitivity of the methods may have been insufficient to reveal very small amounts. On the other hand adrenaline (39) and noradrenaline (40) remain in the cerebrospinal fluid for long periods of time after intrathecal injection.

Occurrence and release from the suprarenal medulla; differentiated secretion. Since the first evidence of the presence of noradrenaline in suprarenals was presented by Holtz et al. in 1947 (34) it has been found in the suprarenal medulla of most animals. While the proportions of adrenaline and noradrenaline vary to a large extent in different animal species, they are relatively constant in the same species (Table II). This makes it difficult to believe that the same cells produce both compounds; in fact it would be strange if species-specific equilibria between the methylated and non-methylated compound were attained. This difficulty is avoided by assuming specific adrenaline and noradrenaline producing cells. Support for this concept is obtained by recently published reports (5, 13, 14, 37) in which a selective secretion of one or the other compound has been observed. Moreover, it has been demonstrated (32) that specific cells in the suprarenal medulla show pigment formation on oxidation with potassium iodate in the same way as noradrenaline in vitro.

The catechol amines in human suprarenals have been estimated in material

TABLE II

Noradrenaline and adrenaline content in suprarenal glands from various species
(Mean figures computed from the literature)

	Noradrenaline mg/g	Adrenaline mg/g	Noradrenaline %
Rabbit	0.02	0.39	4.5
Guinea pig	0.07	0.56	11
Rat	0.16	0.90	16
Zebra	0.23	1.7	13
Horse (medulla)	1.95	8.7	19
Homo (adrenalectomy)	0.09	0.49	16
Macacus radiatus	0.06	0.27	19
Dog	0.48	1.6	24
Cow	1.2	3.1	27
Sheep	0.54	1.1	33
Goat	0.83	1.4	37
Impala	0.21	0.57	28
Grant Gazelle	0.38	0.68	33
Dik-Dik	0.044	0.081	36
Thompson Gazelle	0.36	0.56	39
Pig	0.74	1.0	42
Wildebeest	0.60	0.83	42
Cat	0.51	0.63	45
Lion	0.29	0.24	55
Dogfish	6.0	3.0	33
Toad	1.7	2.0	45
Squirrel	0.10	0.10	50
Pigeon	1.7	1.4	55
Domestic Fowl	7.3	3.1	70
Whale	1.4	0.67	68

obtained by adrenalectomy, the mean figures being 0.49 mg/g adrenaline, and 0.09 mg/g noradrenaline (16).

An interesting shift in the catechol amine distribution of the suprarenals and other chromaffin tissue takes place from fetal to adult life (36, 56). In early fetal life these tissues contain almost entirely noradrenaline, the adrenaline proportion showing a gradual rise towards the adult stage. To assume that the chromaffin cells gradually acquire a methylating power appears less likely, and it would seem more probable that special methylating cells gradually increase in number.

Another example of differentiated production of adrenaline and noradrenaline is offered by the chromaffin cell tumors. Some of these apparently produce and contain only noradrenaline while others produce both compounds, noradrenaline,

however, always appearing in relatively large amounts. It seems most likely that the tumor develops from one or both kinds of cells. However, tumors containing only adrenaline have not been observed.

Functional differentiation between adrenaline and noradrenaline actions. When the actions of adrenaline and noradrenaline are discussed it is paramount to distinguish between the physiologically occurring actions and the effects of what may be termed pharmacological doses. The mode of administration such as by single injections or by continuous infusion is also likely to influence the results considerably.

The differentiated secretion, as mentioned in the preceding section, is consistent with the important differences in action between adrenaline and noradrenaline. The opinion, still sometimes maintained, that noradrenaline and adrenaline are similar in action is only true in part and may lead to serious misconceptions.

Certain similarities in action between the two substances are obvious and it is sufficient to mention their stimulating action on the heart, the constriction in certain vascular areas, and the stimulation of some and relaxation of other smooth muscles. Important quantitative differences occur however: to mention a special case, adrenaline is usually 20–50 times as active as noradrenaline in relaxing the chicken rectal caecum.

Far-reaching differences are present as regards metabolic actions and certain effects on the central and peripheral nervous system. Thus in many branches of metabolic action, such as oxygen consumption (29), glucose output of the liver (1, 35), lactic acid formation and potassium shifts, as well as in actions on white blood cells and adreno-cortical ascorbic acid and cholesterol, adrenaline is usually from 5 to 10 times as active as noradrenaline. Also in the actions on the nervous system marked quantitative differences have been noted. The inhibitory action on ganglionic transmission is thus about 4 times stronger for adrenaline than for noradrenaline (45). Moreover, adrenaline is much more active in inducing electric activity in the hypothalamus (52) and the subjective effects of adrenaline are rather more impressive than those of noradrenaline.

A study of the release of noradrenaline and adrenaline from the adrenergic nerves or from the suprarenal medulla reveals that under such conditions as involve some kind of circulatory stress, noradrenaline is predominantly released. This is the case in erect position and other conditions which involve the activation of carotid sinus pressor reflex (13, 38), heavy muscular work (18), and after acute myocardial infarction (24). Furthermore, an increased secretion of noradrenaline has been observed in a certain proportion of cases of essential hypertension, presumably of the neurogenic type (11). Adrenaline, on the other hand, is released in larger quantities during emotional stimuli (21) or hypoglycemia (5, 20, 37, 50), during pain or after trauma (25). In postural hypotension a low output of noradrenaline may be causally related to the inefficiency of the blood pressure homeostatic mechanisms (43).

Direct hypothalamic stimulation releases either noradrenaline or adrenaline predominantly from the suprarenal medulla according to the site of stimulation (14).

In summary, recent evidence indicates a differentiated secretion of noradrenaline and adrenaline from the catechol amine producing structures (adrenergic nerve terminals, the suprarenal medulla and chromaffin cells in the tissues) depending on the functional requirements of the organism. Thus noradrenaline is released during conditions which involve primarily circulatory needs (blood pressure homeostasis) and the nervous regulation of smooth muscle activity, while adrenaline is primarily engaged in the adjustments of certain metabolic functions and the regional blood supply to organs, and thus complies with the definition given by Cannon as an emergency hormone. Although noradrenaline may be regarded as a tool for maintaining certain homeostatic functions under normal conditions, it is obvious that this substance like adrenaline may also serve as an emergency hormone in the meaning of Cannon.

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