REVIEW

Nervous system and hypertension

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Summary

1. Presynaptic regulation. The regulation of noradrenaline release by a wide variety of substances acting on presynaptic receptors suggests that local factors may play a greater role in the control of blood pressure than was previously believed and that a number of new approaches to the drug treatment of hypertension could be developed. It also raises the possibility that there might be differences in the presynaptic receptor populations of hypertensive and normotensive subjects or animals.

2. Central nerve pathways. There is a need for more precise delineation of central nerve tracts subserving a cardiovascular function and for greater use of morphological techniques to confirm the reliability of biochemical and physiological experiments in the central nervous system. Two appropriate techniques are described.

3. Models of experimental hypertension. (a) Neurogenic hypertension: interference with baroreceptor afferents can cause a permanent elevation of arterial pressure mediated by increased activity of peripheral sympathetic nerves and of descending noradrenergic nerves terminating in the spinal cord. Catecholamine nerve connections of the nucleus tractus solitarius serve mainly to modulate rather than to mediate baroreceptor reflexes. (b) DOCA–salt hypertension: increased peripheral sympathetic activity is important in both the initiation and the maintenance of this form of hypertension. The decrease in brain-stem noradrenaline turnover found in this model could play a determinant role in the development of the high blood pressure. (c) Renal hypertension: both central and peripheral nervous mechanisms contribute to the development and the early phase of ‘one-kidney’ hypertension in animals. Their role in the maintenance of this form of hypertension is still controversial. (d) Spontaneously hypertensive rats: peripheral and central mechanisms do not appear to have a major role in the maintenance of this form of hypertension. However, it seems possible that centrally evoked increases in peripheral sympathetic activity could be important in the initiation of the high blood pressure. (e) Central catecholamines and blood pressure control: central catecholaminergic nerves do not make up a single homogeneous system. For example, the activity of descending noradrenergic nerves in the spinal cord contributes to an elevation of arterial pressure, whereas the activity of catecholaminergic nerves in the dorsomedial medulla appears to have a depressor effect.

4. Human essential hypertension. (a) There is no good evidence that the nervous system plays the major primary role in the development or maintenance of essential human hypertension. (b) Effective treatment of raised blood pressure through nervous mechanisms requires an understanding of the factors that normally control the pressure and does not necessarily depend on reversing specific nervous processes responsible for producing the increase in pressure.

Key words: catecholamines, control of blood pressure, DOCA–salt hypertension, essential hypertension, experimental hypertension, histochemical fluorescence, neurogenic hypertension, noradrenaline release, noradrenergic neurons, pathogenesis of hypertension, presynaptic receptors, renal hypertension, spontaneous hypertensive rat.

Abbreviations: DOCA, deoxycorticosterone acetate; SH rats, spontaneously hypertensive rats.
Substances that can decrease the amount of noradrenaline released by a nerve impulse include noradrenaline itself acting on an α-adrenergic receptor, acetylcholine acting on a muscarinic receptor, histamine acting on a histamine-H₁ receptor, encephalins acting on an ‘opiate’ receptor, prostaglandins of the E series, dopamine, adenosine and 5-hydroxytryptamine. Substances that can facilitate the release of noradrenaline include noradrenaline and adrenaline acting on a β-adrenergic receptor, acetylcholine acting on a nicotinic receptor and angiotensin II (Fig. 1).

It is evident that noradrenaline release is not regulated only by variation in impulse rate, but is subject to modulation by a variety of mechanisms acting on the synapse. Therefore, in considering the intact organism, it seems likely that the transmission of information is subject to considerable local influence.

Implications for control of blood pressure

1. Most of the presynaptic receptors described to date have been discovered in the peripheral nervous system, but it is clearly possible that many may also be present in the central nervous system. So far there is evidence for both α- and β-adrenoceptive prejunctional receptors in the central nervous system.

2. It is most unlikely that all the prejunctional receptors described above will be found in all peripheral noradrenergic nerves. Rather, it seems likely that some of these prejunctional receptors will only be found to have functional significance in certain restricted outflows of the peripheral autonomic nervous system.

3. Whenever a group of impulses conveying cardiovascular information is en route within the central nervous system, presynaptic regulation provides a new and additional mechanism for modifying that information and interacting with other nerves at central noradrenergic synapses (Fig. 2).

4. The potential presence of a wide variety of prejunctional receptors on peripheral noradrenergic synapses suggests that local and regional factors may have a greater influence on the level of sympathetic activity, and ultimately blood pressure, than previously believed. Thus differences in the nature of presynaptic receptors present in various beds, as well as differences in local chemicals produced by different tissues, could profoundly modify the effects of impulses travelling...
down sympathetic noradrenergic nerves to different regional beds.

5. It is possible that either the number or the sensitivity of some prejunctional receptors could be different in hypertensive humans or animals, compared with their normotensive counterparts.

6. The great diversity of prejunctional receptors modulating noradrenaline release paves the way for a variety of new pharmacological approaches to the drug treatment of high blood pressure.

Identification of central neurons involved in control of blood pressure

Many groups studying central control of blood pressure are currently making discrete 'nuclear' lesions, injecting drugs into 'specific' loci, and assaying amines and enzymes in minute areas of the central nervous system. Yet many of these groups have at no stage obtained histological confirmation that their techniques are sufficiently accurate to identify the specific loci required. This is in part due to the laborious nature of the traditional histochemical fluorescence (Falck-Hillarp) method for identification of catecholamine-containing neurons, a method which has played a major role in stimulating interest in this field.

Novel and simple methods now available have much to offer in this area. One is the formaldehyde–glutaraldehyde fluorescence method of Furness, Costa & Wilson (1977), which has now been applied to the central nervous system (Furness, Costa & Blessing, 1977; Blessing, Chalmers & Howe, 1978). This method utilizes perfusion of the brain in situ at room temperature with a mixture of formaldehyde and glutaraldehyde that serves both to fix the brain in situ and simultaneously to convert catecholamines into fluorescent derivatives visible under the fluorescence microscope (Fig. 3). One of the chief advantages of this method is that it is a standard technique for fixation of tissues for electron microscopy, so that fluorescence and electron microscopy can be utilized on the same tissue section. Another is its simplicity and speed, in that only 1–1·5 h are necessary from the start of perfusion to visualization of catecholamine fluorophores under the microscope.

Another very useful method is the horseradish peroxidase method for retrograde tracking of cell bodies (La Vail, 1975). This method depends on the retrograde transport of an enzyme, horseradish peroxidase, which is taken up by nerve endings and transported to cell bodies, where it can be identified by reaction with suitable cytochemical substrates.

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**Fig. 2.** Schematic representation of central descending neurons through brain stem and cord and also showing peripheral pre- and post-ganglionic sympathetic neurons with a noradrenergic neuroeffector junction (NA). The potential for presynaptic regulation at noradrenergic synapses is shown by the rings of arrows.

**Fig. 3.** Photomicrograph of fluorescent catecholamine-containing cells in (a) area A₁ in the ventrolateral medulla and (b) area A₂ in the dorsomedial medulla. Lines show 25 μm.
The horseradish-peroxidase method is not specific to any particular group of neurotransmitters such as catecholamines and can be used to track any nerve cell in the central nervous system. The specific tracking of catecholamine-containing cells in the central nervous system can be achieved by combining the peroxidase method with a modification of the formaldehyde–glutaraldehyde method, as recently described (Blessing, Furness, Costa & Chalmers, 1978).

Models of experimental hypertension in animals

Neurogenic hypertension produced by lesions of arterial baroreceptor afferents

It has long been known that arterial pressure can be increased by inactivation of the afferent limb of the arterial baroreceptor reflexes, which are illustrated schematically in Fig. 4. In the periphery, this elevation in arterial pressure is mediated by increased activity of sympathetic noradrenergic neurons (De Quattro, Nagatsu, Maronde & Alexander, 1969). Within the central nervous system, the pathways followed by catecholaminergic nerves are similar to those of neurons subserving central cardiovascular control, and there is good evidence that some of the neurons participating in the regulation of arterial pressure do in fact utilize catecholamines as neurotransmitters (Chalmers, 1975a,b,c; Chalmers, White, Geffen & Rush, 1977).

Experiments in rabbits have shown that sino-aortic denervation produces a selective increase in noradrenaline turnover in the hypothalamus and the thoracolumbar cord (Chalmers & Wurtman, 1971; Fig. 5). The increase in hypothalamic noradrenaline turnover in this situation is consistent with the concept that baroreflex function utilizes neural loops at suprabulbar levels. The
selective increase in noradrenaline turnover in the thoracolumbar cord is consistent with an increase in the activity of descending noradrenergic tracts terminating in the sympathetic lateral horn. This is supported by the finding that the activity of tyrosine hydroxylase is also selectively increased in this region of the cord (Fig. 5). It is further supported by the finding that destruction of central catecholaminergic nerves by intracisternal administration of 6-hydroxydopamine does in fact prevent and reverse the neurogenic hypertension produced by sinoaortic denervation in the rabbit (Chalmers & Reid, 1972). Therefore it seems likely that the arterial baroreceptor reflexes work by restraining the activity of descending noradrenergic nerves whose activity tends to facilitate the maintenance and elevation of arterial pressure.

The degree of depletion of catecholamine stores achieved by 6-hydroxydopamine can be critical, as demonstrated by experiments in which intracisternal administration of 600 µg/kg successfully abolished neurogenic hypertension whereas 200 µg/kg did not affect the pressure (Chalmers & Reid, 1972); the point to note is that the higher dose reduced the noradrenaline concentration in the spinal cord to less than 10% of control values whereas the lower dose reduced it to only around 25–30% of control (Fig. 6). The difficulty with the administration of 6-hydroxydopamine into the cerebrospinal fluid is that it has many non-specific effects and causes a deterioration in the general condition of the animals, which can limit the degree of noradrenaline depletion to such an extent that few conclusions can safely be drawn from negative results. Furthermore, in some cases where administration of 6-hydroxydopamine into the cerebrospinal fluid has failed to prevent changes in pressure (Hauesler, 1976; Korner, 1976), the experimental situation has been a very different one involving the administration of a strong phasic input to central cardiovascular neurons. In these circumstances it is entirely possible that surviving noradrenergic neurons may be recruited, or that alternative neural pathways, utilizing different neurotransmitters (for example, serotonin), could compensate for the loss of one particular group of nerves.

Doba & Reis (1973, 1974) have made similar observations in a different model of neurogenic hypertension produced by central deafferentation of the baroreflexes with bilateral stereotactic lesions of the nucleus tractus solitarius in the rat. Acute nucleus tractus solitarius hypertension is very much more severe than buffer nerve hypertension and may lead to death from cardiac failure within hours (Doba & Reis, 1973). This form of hyper-
Mean arterial pressure (mmHg)

FIG. 7. Frequency distribution curves of mean arterial pressure in control and 6-hydroxydopamine-treated rats. (a) Overlay of results for five control rats 4 days after vehicle solution (0.8 mg of ascorbic acid/ml) was microinjected into the nucleus tractus solitarius. (b) Overlay of results for five rats 4 days after 6-hydroxydopamine (4 μg in 1 μl) was microinjected into the nucleus. The lability of the pressure is increased after injection with 6-hydroxydopamine (from Reis et al., 1977).

tension is dependent upon the intactness of supra-pontine structures and is abolished by decerebration (Reis, Doba & Nathan, 1976). The afferent and efferent connections of the nucleus in relation to the baroreflex arc have been accurately described (Palkovits & Zaborszky, 1977) and the effects of acute and chronic lesions at different levels of the nucleus on arterial pressure have been carefully documented (De Jong, Zandberg, Palkovits & Bohus, 1977).

Doba & Reis (1974) confirmed that intracisternal administration of 6-hydroxydopamine could prevent the development of nucleus tractus solitarius hypertension, supporting the concept that it is dependent upon central noradrenergic neurons. In initial experiments utilizing micro-injections of 6-hydroxydopamine to produce selective destruction of noradrenergic nerve terminals in the nucleus, Reis and co-workers found that this procedure caused a transient elevation of arterial pressure lasting approximately 10 days (Doba & Reis, 1974). In subsequent experiments with more refined techniques they demonstrated that selective destruction of only the catecholaminergic nerve endings in the nucleus tractus solitarius did not lead to persistent hypertension of the sort produced by electrolytic lesions in this nucleus (Reis et al., 1976; Reis, Doba, Snyder & Nathan, 1977) but did result in a state of prolonged 'labile hypertension' and vascular hyper-reactivity (Fig. 7). Reis (1978) has recently shown that destruction of area 'A1', an area rich in catecholamine-containing cell bodies and closely related to the nucleus tractus solitarius, produces similar effects. It seems likely that specific destruction of catecholaminergic nerves originating in area 'A1' and terminating in the nucleus contributes more to increased lability than to increased arterial pressure (Fig. 7). These catecholaminergic neurons (which are probably noradrenergic) probably serve more to modulate than to mediate baroreceptor reflexes, by facilitating the role of baroreceptors in stabilizing the arterial pressure (Reis, 1978; Reis et al., 1976, 1977).

In summary, interference with baroreceptor afferents by section of buffer nerves or lesions of the nucleus tractus solitarius can cause permanent neurogenic hypertension. The elevated pressure in this model is mediated by increased activity of peripheral sympathetic nerves and descending noradrenergic nerves terminating in the spinal cord. Catecholamine nerve connections of the nucleus tractus solitarius serve mainly to modulate rather than mediate baroreceptor reflexes.

DOCA-salt hypertension

There is now a large body of evidence from De Champlain, Axelrod and colleagues that both adrenal medullary activity and peripheral sympathetic neural activity to the heart and blood vessels are increased in DOCA-salt hypertension (De Champlain, 1972). It has been established that the increase in peripheral noradrenaline turnover rate is accompanied by a reciprocal decrease in the turnover of noradrenaline in brain stem and hypothalamus (Nakamura, Gerold & Thoenen, 1971; Van Ameringen, De Champlain & Imbeault, 1977; Fig. 8). Activities of the enzyme phenylethanolamine N-methyltransferase, which is probably a marker for adrenaline-containing cells in the brain, are also increased in the A1 region of adult DOCA-salt-hypertensive rats (Grobecker, Saavedra, Roizen, Weise, Kopin & Axelrod, 1976).

In this model it has been established that prior
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The multiplicity of models available makes this field a complex one but overall there is good evidence for participation of the nervous system in the pathogenesis of the one-kidney model. Peripheral noradrenergic mechanisms in this form of experimental hypertension appear to be similar to those observed in DOCA–salt hypertension. In rats made hypertensive by unilateral renal wrapping with contralateral nephrectomy (Volicer, Scheer, Hilde & Visweaswaram, 1968) or by partial unilateral infarction with contralateral nephrectomy (Henning, 1969), there is an increase in the activity of peripheral sympathetic nerves to the heart and blood vessels. Plasma noradrenaline concentration is also elevated in the first month after unilateral renal artery constriction if accompanied by contralateral nephrectomy (one-kidney model) but is not altered if the contralateral kidney is left in situ (Reid, Dargie, Franklin & Fraser, 1976; Dargie, Franklin & Reid, 1977).

Although no changes have been reported in the concentration or turnover rate of noradrenaline in whole brain or spinal cord (Henning, 1969; Chalmers, Dollery, Lewis & Reid, 1974) more recent observations with micro-assays have demonstrated important changes in the central nervous system. Petty & Reid (1977) have reported decreases in noradrenaline concentrations in a number of discrete nuclei 72 h after unilateral renal clip with contralateral nephrectomy. Significant decreases in noradrenaline concentrations were found at this time in the nucleus tractus solitarius and the lateral reticular nucleus in the medulla and in the anterior, posterior and periventricular hypothalamic nuclei. These authors have also reported decreases in tyrosine hydroxylase activity in the same three hypothalamic nuclei at 72 h (Petty & Reid, 1978) as well as increases in phenylethanolamine N-methyltransferase activity in the nucleus tractus solitarius and locus coeruleus in this model.

Ablation of peripheral sympathetic nerves by immunosympathectomy or by intravenously injected 6-hydroxydopamine will prevent this form of hypertension, particularly if combined with adrenalectomy, though it will only partially reverse the high pressure in animals with established renal

ggested that the decreased noradrenaline turnover in the brain stem may have a determinant role in the development of this form of hypertension (Van Ameringen et al., 1977).

Experimental renal hypertension

Fig. 8. Endogenous noradrenaline concentration of (a) brain stem and (b) intestine before (0 h), 4 h and 8 h after administration of α-methylparatyrosine to normotensive (●) and DOCA–salt-hypertensive (○) animals. Values are expressed as percentages of initial concentrations obtained at 0 h (from Van Ameringen et al., 1977).

Treatment with 6-hydroxydopamine given into the cerebrospinal fluid can prevent the development of hypertension (Hauesler, Finch & Thoenen, 1972; Myers et al., 1974; Reid, Zivin & Kopin, 1975). On the other hand, the cerebroventricular administration 6-hydroxydopamine to rats with established DOCA–salt hypertension does not reverse the hypertension (Hauesler, Gerold & Thoenen, 1972), so that the destruction of central catecholaminergic nerves with 6-hydroxydopamine seems to be more effective in preventing the development of this form of hypertension than in abolishing the hypertension once established. However, recent experiments by De Champlain and co-workers have shown that transection of the spinal cord in animals with DOCA–salt hypertension reverses the hypertension and the increased turnover of noradrenaline in heart and intestine (Fig. 8), but has no effect on the decreased turnover in the brain stem, which persists unchanged. This clearly demonstrates the importance of nervous mechanisms in DOCA–salt hypertension and it has been sug-
In summary, it is clear that both central and peripheral nervous mechanisms contribute to the development and the early phases of one-kidney renal hypertension in animals. It seems that, under some experimental conditions, these mechanisms can also participate in the maintenance of this form of hypertension.

**Spontaneously hypertensive (SH) rats**

Early studies with this model were complicated by lack of appropriate controls, so that many initial reports of decreased central and peripheral adrenergic nerve activity have had to be re-interpreted and are now attributed, at least in part, to genetic variation independent of blood pressure (Lovenberg, Yamabe, De Jong & Hansen, 1973). There is now a great deal of evidence to suggest that increased sympathetic activity contributes to the initiation of hypertension in young SH rats. Okamoto, Yamori and co-workers have demonstrated increases in cardiac noradrenaline turnover and in splanchnic sympathetic discharge in young SH rats (Okamoto, Nosaka, Yamori & Matsumoto, 1967; Yamori, 1974, 1976). They have also shown that these changes in cardiac noradrenaline turnover are abolished by 15 weeks of age (Yamori, 1976). It has also been shown that plasma noradrenaline concentrations and dopamine-β-hydroxylase activities are increased in the young SH rats, even though adrenal tyrosine hydroxylase, dopamine β-hydroxylase and phenylethanolamine N-methyltransferase activities are decreased, suggesting that the increased activity resides in peripheral sympathetic noradrenergic nerves (Grovecker et al., 1976; Nagaoka & Lovenberg, 1976). More recently, it has been reported that cardiac noradrenaline concentration and storage capacity is reduced in older SH rats and more particularly in the 'stroke-prone' SH rats (Howe, Provis, West & Chalmers, 1978).

In the central nervous system it has been found that phenylethanolamine N-methyltransferase activity is raised specifically in areas A1 and A2 of the medulla oblongata of young SH rats but not in adult SH rats (Saavedra, Grovecker & Axelrod, 1976). Increased amounts of endogenous noradrenaline, adrenaline and dopamine have been reported in area A2, and of noradrenaline in area A1 (Versteeg, Palkovits, Van der Gugten, Wijnen, Smeets & De Jong, 1977). More recently increases in noradrenaline concentration, more marked in young rats, have been found in the spinal cord and
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(a) Cerebellum

(b) Spinal cord

Fig. 10. Endogenous noradrenaline concentration in (a) cerebellum and (b) spinal cord of □, WKY rats (Wistar–Kyoto control rats), ■, SH rats and ▶, stroke-prone SH rats at three different ages (3–6 weeks, 14–19 weeks and over 31 weeks). (Unpublished observations.)

Ablation experiments with intravenously administered 6-hydroxydopamine to neonatal SH rats to produce a neonatal sympathectomy also prevented the development of hypertension (Provooost, Bohus & De Jong, 1977).

In summary, there is little evidence to suggest that nervous mechanisms play a major primary role in the maintenance of hypertension in SH rats. On the other hand, it is possible that peripheral and central sympathetic mechanisms play an important role in the initiation of this form of experimental hypertension and that the initial hyperactivity of peripheral sympathetic nerves may be centrally evoked.

Central catecholaminergic nerves and blood pressure control

It is important to appreciate that the central catecholamine-containing neurons participating in blood pressure control do not represent a homogeneous system, any more than does the peripheral sympathetic system. It is now accepted that some central catecholaminergic nerves act to elevate or maintain arterial pressure whereas others have a depressor effect. The only real difficulty lies in defining the facilitatory and inhibitory systems more precisely anatomically and functionally.

In my view, the catecholaminergic descending neurons in the spinal cord and ending in the sympathetic lateral columns form part of one system whose activity leads to elevated arterial pressure; these particular catecholaminergic nerves are probably noradrenergic. On the other hand, catecholaminergic nerves in the dorso–medial medulla, around area A1 and the nucleus tractus solitarius, appear to participate in a system whose activity tends to depress arterial pressure and also to modulate baroreceptor reflexes, possibly by inhibiting the activity of the descending spinal neurons; the catecholaminergic nerves in the medulla could well include adrenaline-releasing nerves as well as nerves releasing noradrenaline.

Nervous system and clinical essential hypertension

The nervous system plays a key role in the regulation of the circulation. In fact it is probably the most important means available for controlling blood pressure, whether normal or raised. On the other hand, there is clearly insufficient evidence that a derangement in the function of the nervous system plays the dominant primary role in the aetiology or pathogenesis of essential hypertension.
in humans. Although it is possible that nervous mechanisms play a more significant role in the initiation of hypertension than in its maintenance, this, too, has yet to be established.

Nervous mechanisms are clearly very important in considering the treatment of high blood pressure in humans. In fact, much of the research into nervous mechanisms was kindled by the development of drugs like reserpine, guanethidine, methyldopa and clonidine which have lowered pressure effectively through actions on either the peripheral sympathetic system or on the central nervous system. However, there is once again no evidence that the increase in pressure in the patient with hypertension is produced through mechanisms that are qualitatively different from those operating in the normal subject as depicted in Fig. 11(a). Thus, in treating high blood pressure, it is certainly not essential to direct therapy at this hypothetical ‘abnormal’ component; after all, even if it existed, pressure could be lowered just as effectively by reducing the ‘normal’ component. However, if we accept that the mechanisms controlling pressure are qualitatively the same in those with high and those with normal pressure (Fig. 11b), the most important basis for the treatment of high blood pressure will remain a good understanding of the processes that control blood pressure in the normotensive population. It may be well to remember, as pointed out by Pickering (1968), that hypertension is a quantity not a quality, that the distribution of blood pressure throughout the total population is unimodal and not bimodal, and that the population with hypertension merges imperceptibly with the ‘normal’ population.

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