Central catecholaminergic nerves have an integral place in the central connections of the autonomic nervous system, and they play an important role in the regulation of arterial blood pressure (1-19). Some evidence suggests that central serotonergic nerves also participate in the control of blood pressure (19-24). Studies in various models of experimental hypertension have demonstrated changes in the metabolism and the activity of these central monoaminergic nerves (3, 9, 13, 24). In addition, selective ablation of central catecholaminergic or serotonergic nerves with a variety of chemical compounds profoundly modifies the development of high blood pressure in a number of experimental models (7, 8, 10, 11, 17, 23, 24). It seems clear that central monoaminergic systems participate in the regulation of normal blood pressure and that their function is altered in experimental hypertension. However, the exact significance of these changes in experimental hypertension has not been established. Moreover, it is not yet clear which changes are of primary causal importance and which are secondary in nature.

The development of histochemical fluorescence methods for cellular localization of biogenic amines has facilitated the mapping of specific catecholaminergic and serotonergic tracts in the central nervous system (CNS) (25-27). During the last decade it was widely held that only two catecholamines were important neurotransmitters in the CNS—dopamine in the basal ganglia and limbic systems and norepinephrine more diffusely. There is now good evidence from new immunohistochemical methods (28) and sensitive biochemical assays (29) that epinephrine is also a central neurotransmitter. Since many of the studies on brain amines and blood pressure regulation have not differentiated between dopamine, norepinephrine, and epinephrine, the term catecholaminergic will be used in this review to cover all three amines as a group and the terms dopaminergic, noradrenergic, and adrenergic, respectively, will be used to cover each one specifically. I emphasize that the term adrenergic will not be used to refer generically to all catecholamines.

The pathways followed by central noradrenergic, adrenergic, and serotonergic neurons are strikingly similar to central pathways involved in cardiovascular regulation (30, Figs. 1 and 2). The cell bodies of these three monoaminergic systems are found predominantly in the brainstem. From here, some axons ascend to ramify in the brain; particularly high concentrations of nerve endings are found in the hypothalamus and the reticular formation. Other axons descend in the spinal cord.

The recently described adrenergic neurons terminate abundantly around the nucleus of the tractus solitarius (NTS) and the locus ceruleus in the brainstem. Descending noradrenergic and adrenergic nerves appear to arise from two main areas in the brainstem. One of these areas, called “group A1” by Dahlstrom and Fuxe (25), seems to coincide with the vasopressor areas in the ventrolateral part of the medulla, and the other area, called “group A2,” probably corresponds with the NTS and the vagal complex. Descending serotonergic nerves appear to arise from “group B1” and “group B2” in the midline nuclei, and “group B3” arises more laterally. These three groups of descending monoaminergic neurons travel down the lateral funiculi of the cord to terminate in the grey matter of the cord with a particularly high density of fluorescent nerve endings in the sympathetic intermediolateral cell columns between the first thoracic and second lumbar segments. These nerve endings appear to make intimate contact with sympathetic preganglionic neurons or with the network of abundant interneurons that surrounds them. Descending serotonergic fibers also terminate densely in the...
SYMPATHETIC PREGANGLIONIC FIBRES

HYPOTHALAMUS

FIGURE 1

Simplified schematic representation of central monoaminergic pathways showing cell bodies in the brainstem with axons either ascending into the brain or descending into the spinal cord.

lumbar parasympathetic nuclei. This arrangement of central monoaminergic nerves is clearly well suited to the mediation of autonomic and cardiovascular information.

METHODS USED TO STUDY THE ROLE OF MONOAMINERGIC PATHWAYS IN THE CONTROL OF CIRCULATION AND IN EXPERIMENTAL HYPERTENSION

The presence of suitably located monoaminergic pathways falls a long way short of proving their participation in a particular function such as the regulation of arterial blood pressure. The methods which have been used to try to demonstrate the involvement of central monoaminergic neurons in cardiovascular control include (1) administration of adrenoceptive agonists and blockers into the cerebrospinal fluid (CSF), (2) electrical and iontophoretic stimulation of CNS regions rich in amines, with recording of distal evoked potentials and blood pressure, (3) measurement of metabolism and turnover of monoamines and activity of related enzymes after the production of experimental hypertension, and (4) intrathecal or systemic administration of chemicals that selectively impair the function of or actually destroy a particular group of monoaminergic nerves in normal animals and in animals with experimental hypertension.

The administration of adrenoceptive agonists and blockers into the CSF has been reported to produce a multiplicity of different cardiovascular responses. Drugs such as epinephrine, norepinephrine, and isoprenaline have been variously reported to cause rises or falls in blood pressure, and the responses have been variously attributed to alpha- or beta-adrenoceptive mechanisms (30-36). These difficulties arise in part from the great variation in dose and in site and mode of administration, in part from the variation in species, and in part from the use of anesthetized preparations in some cases and conscious animals in others.

The use of electrical and iontophoretic stimulation of specific nerve tracts in the CNS has one great advantage: these methods allow precision in defining a tract's inputs and outputs and precision
in demonstrating that a particular response such as an increase or a decrease in blood pressure can be evoked. Iontophoretic application of minute quantities of norepinephrine, serotonin, or acetylcholine to particular neurons has demonstrated that each of these transmitters can evoke facilitatory or inhibitory responses (37, 38). The disadvantage of these methods is that they can only outline the pathways that are potentially capable of mediating a given function. They cannot demonstrate that a particular central pathway actually does participate in this function in a physiological situation in the intact organism.

Studies of the metabolism of neurotransmitters and their related enzymes in the CNS of animals with experimental hypertension have the advantage of providing information about changes that actually occur in intact animals with a particular experimental form of high blood pressure. However, there are several disadvantages associated with these methods. (1) The biochemical data must be extrapolated to assess changes in the physiological activity of nervous pathways, although there is probably sufficient evidence to justify this extrapolation (39-41). (2) These methods inherently lack precision, since available techniques depend on measuring average changes in regions as large as the brainstem or the hypothalamus, each of which may contain many populations of monoaminergic neurons subserving different or even opposing functions. Thus, changes in small groups of critically important neurons may well be partially or totally masked. (3) The demonstration of changes in amine metabolism does not prove that these changes play a primary role in mediating changes in arterial blood pressure; the metabolic changes could be secondary phenomena.

The fourth method that has been extensively used is the administration of chemical ablators of a particular monoaminergic system, such as 6-hydroxydopamine (6-OH-DA) to destroy central noradrenergic nerves or 5,6-dihydroxytryptamine (5,6-DHT) to destroy central serotonergic nerves. Other agents used include the synthesis inhibitors p-chlorophenylalanine (pCPA) and alphamethylparatyrosine. The advantage of this method is that it can link the ablation of a specific neurotransmitter system in the CNS with particular physiological changes such as an alteration in arterial blood pressure. The disadvantages are (1) that these drugs act widely on all nerves of the particular transmitter type selected not just on the specific tracts being studied and (2) that these drugs are only relatively selective and have many unwanted nonspecific effects on other neurons and other organs.

**ROLE OF CENTRAL MONOAMINERGIC NERVES IN THE MAINTENANCE OF RESTING BLOOD PRESSURE IN NORMOTENSIVE ANIMALS**

**Catecholaminergic Nerves.**—Selective ablation of central catecholaminergic nerves can be achieved by intrathecal administration of 6-OH-DA, a drug that causes selective degeneration of catecholaminergic nerve endings and depletion of their transmitter stores. Adrenergic neurons are relatively resistant to the actions of 6-OH-DA, which has much greater effects on noradrenergic nerves, particularly, and on dopaminergic nerves. Small doses of this drug given intrathecally have the advantage that their effects are very unlikely to be due to actions on peripheral sympathetic nerves and are more likely to be mediated centrally. This situation obtains partly because 6-OH-DA does not readily cross the blood-brain barrier and partly because the doses given are too small to produce sustained systemic effects (8, 10).

Administration of 6-OH-DA into the CSF of normal animals produces a very brief (5-minute) increase in arterial blood pressure, which is only seen in unanesthetized animals (42), followed by a fall in blood pressure lasting a few hours (8, 10, 42). This biphasic response parallels the effects of intravenously administered 6-OH-DA. The immediate increase in blood pressure is probably due to the release of the transmitter norepinephrine, and the subsequent transient fall in blood pressure is probably due to direct stimulation of central inhibitory alpha-adrenoceptive nerves by 6-OH-DA itself (5, 8), leading to a transient withdrawal of peripheral alpha-adrenergic vasoconstrictor tone (8, 10).

Permanent ablation of central catecholaminergic nerves by intracisternal administration of 6-OH-DA has no long-term effects on the arterial blood pressure of normotensive animals (8, 10, 17). On the other hand, ablation of the peripheral sympathoadrenal axis by combined chemical sympathectomy and adrenalectomy causes a significant lowering of arterial blood pressure in both rats and rabbits (14, 15, 43). Thus, it seems that the slight tonic activity which the peripheral sympathoadrenal system exerts on the circulation of conscious normotensive animals at rest (30) is not dependent on the tonic activity of central catecholaminergic nerves. It may, however, be dependent on the tonic activity of central serotonergic nerves, as discussed subsequently.

The administration of 6-OH-DA into the CSF

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does cause a reduction in heart rate of about 30% (8, 10, 17) which lasts as long as observations have been continued (up to 3 weeks) (8, 10). Analysis of this bradycardia using intravenously administered blocking agents has shown that in the periphery it is mediated mainly by an increase in vagal activity, since it can be completely abolished by atropine (10, 17). It is probably also partly due to a reduction of peripheral cardiac sympathetic activity, since it is reduced but not abolished by prior intravenous administration of propranolol (10).

Centrally administered 6-OH-DA appears to destroy central catecholaminergic nerves that normally inhibit the vagus and thus cause a bradycardia by central vagal disinhibition. It also seems to destroy bulbospinal catecholaminergic nerves, probably noradrenergic, that normally facilitate the action of sympathetic preganglionic cardiac neurons (Figs. 2 and 3). The inhibitory fibers acting on the vagus are probably contained entirely within the brainstem, since there are few if any long descending noradrenergic neurons in the brain. The inhibitory fibers probably do not terminate on the primary baroreceptor synapse in the NTS, since lesions of the NTS do not cause a bradycardia (16), but on a secondary synapse beyond the NTS (Fig. 3).

Serotonergic Nerves.—Studies on the role of central serotonergic nerves in the regulation of arterial blood pressure are few and conflicting. Reduction of central serotonin stores produced by intraperitoneal and intracisternal administration of pCPA has been reported to cause an increase in systolic arterial blood pressure in rats (20). On the other hand, a similar reduction of central serotonin stores by intraperitoneal administration of pCPA in rabbits (24) and by oral administration of pCPA in rats (44) has been shown to cause a fall in mean arterial blood pressure. In the same way, intravenously administered 5-hydroxytryptophan (5-HTP), a precursor of serotonin that causes an increase in endogenous levels of serotonin (45), has been reported to cause a fall in blood pressure in rats (20) and in anesthetized dogs treated with monooamine oxidase inhibitors (22) and an increase in blood pressure in conscious dogs (21).

Intracisternal administration of 5,6-DHT causes a selective degeneration of serotonergic nerve endings with depletion of serotonin stores in the spinal cord (23, 46, 47) and results in a lowering of mean arterial blood pressure and heart rate in conscious normotensive rabbits and conscious rabbits with neurogenic hypertension (23). This finding suggests that bulbospinal serotonergic nerves have facilitatory effects on arterial blood pressure. Yet, here again, experiments in anesthetized cats have indicated that electrical stimulation of midline medullary vasodepressor centers evokes a discharge from preganglionic sympathetic rami which can be inhibited by 5-HTP; this finding suggests that serotonergic bulbospinal fibers have an inhibitory effect on sympathetic discharge (19). It is possible, of course, that the cells being stimulated were short inhibitory brainstem neurons synapsing with descending bulbospinal nerves rather than the bulbospinal nerves themselves.

Many factors could contribute to this controversy. First, the use of anesthetized preparations can greatly distort the investigation of central mechanisms and should be avoided when possible.
(30, 38). Since some of the biggest reported discrepancies have occurred within the same animal (the rat), it is unlikely that species differences are responsible. The biggest causes of disagreement probably reside in variation in the dose, route, site, and method of administration of the compounds used, in variation in the mode of action of these compounds, and in the lack of true specificity, as discussed more fully subsequently.

**EXPERIMENTAL NEUROGENIC HYPERTENSION**

The key to the function of arterial baroreceptor reflexes lies in the reciprocal relationship between afferent traffic and efferent bulbospinal and peripheral sympathetic activity (30, Fig. 2). The central pathways are polysynaptic, with the primary synapse in the NTS and an inhibitory neuron interposed between the NTS and the cell bodies of bulbospinal fibers originating in the vasomotor areas (30). The simplest way to draw this system is shown in Figure 2, although there are many more interneurons and synapses.

Deafferentation of the arterial baroreceptor reflexes eliminates these inhibitory influences and leads to an increase in the activity of peripheral sympathetic nerves and a long-lasting increase in arterial blood pressure known as neurogenic hypertension (30, 48). Neurogenic hypertension is characterized by wide fluctuations in arterial blood pressure, which increases most in response to stimulation (49). The role of brain amines has been examined in two forms of experimental neurogenic hypertension, the first being produced by bilateral section of the carotid sinus and aortic nerves (9, 10, 23, 24) and the second by central deafferentation following bilateral lesions of the NTS (16, 17).

**Catecholaminergic Nerves.**—There is now good evidence that descending noradrenergic bulbospinal fibers form an essential central link in the baroreceptor reflex arc (Figs. 1 and 2). The evidence for this concept comes from the demonstration that sinoaortic denervation in the rabbit produces selective increases in the turnover of intracisternally administered tritiated norepinephrine and the activity of tyrosine hydroxylase in the thoracolumbar segments of the spinal cord (9). It has also been shown that destruction of central catecholaminergic neurons with intracisternally administered 6-OH-DA, which has its predominant effect in the spinal cord (9) and by lesions of the NTS (17). These experiments suggest that the activity of bulbospinal catecholaminergic nerves facilitates a rise in blood pressure. It is likely that the particular nerves involved are the noradrenergic bulbospinal nerves, since adrenergic nerve endings are relatively resistant to destruction by 6-OH-DA.

Doba and Reis (17) have shown that, whereas intracisternally administered 6-OH-DA abolishes NTS hypertension, local injection of 6-OH-DA into the NTS of rats produces an increase in arterial blood pressure lasting about 14 days. They have pointed out that, whereas the activity of bulbospinal noradrenergic neurons appears to facilitate an increase in pressure, the activity of catecholaminergic neurons affected by local administration of 6-OH-DA in the NTS appears to oppose an increase in blood pressure. Since the NTS contains both catecholaminergic cell bodies and catecholaminergic nerve endings (26), the hypertension produced by 6-OH-DA injected in the NTS could be explained in two ways. First, it could be due to destruction of inhibitory catecholaminergic interneurons originating in the NTS and ultimately synapsing with descending vasomotor nerves (Fig. 4A); such a mechanism of action might

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**FIGURE 4**

Schematic representation of changes in central neural activity leading to neurogenic hypertension. Section of baroreceptor afferents (minuses) or lesions of the NTS lead to a decrease in the activity of inhibitory bulbar fibers between the NTS and the VMC (minuses), hence, an increase in the activity of bulbospinal catecholaminergic fibers (pluses) synapsing with the sympathetic nervous system (pluses) occurs. A and B show two alternative arrangements of catecholaminergic neurons (CA) within this scheme. In both A and B, there are facilitatory bulbospinal catecholaminergic fibers. In A, the inhibitory neuron from the NTS to the VMC is catecholaminergic. In B, a bulbar neuron terminating in the NTS is catecholaminergic; this neuron synapses with an alpha-adrenoceptive inhibitory neuron (a) between the NTS and the VMC. Deafferentation also causes a decrease in efferent vagal activity (minuses) contributing to the tachycardia. Notation is the same as it is in Figure 2.
explain the transient nature of the hypertension, since catecholaminergic cell bodies are more resistant to the effects of 6-OH-DA than are nerve endings. Alternately, it could be due to destruction of catecholaminergic nerve endings, either noradrenergic or adrenergic, terminating in the NTS and synapsing with the inhibitory interneurons (Fig. 4B) through adrenergic receptors on their cell bodies. The latter arrangement would help to explain the mode of action of clonidine, an alphadrenergic agonist that lowers arterial blood pressure by activation of baroreceptor pathways (6, 50).

Doba and Reis (16) have also shown that midcollicular decerebration abolishes NTS hypertension, suggesting that the elevated blood pressure depends on the activity of descending suprabulbar pathways. Such pathways clearly terminate somewhere other than the NTS and are probably not noradrenergic, since no long descending catecholaminergic neurons are thought to be in the brain (25, 26).

Serotonergic Nerves.—The only studies reported so far on changes in central serotonin metabolism in neurogenic hypertension have shown that sinoaortic denervation causes a selective increase in endogenous levels of serotonin and 5-hydroxyindoleacetic acid in the medulla-pons and the thoracolumbar region of the spinal cord; no significant changes occurred in the six other areas of the brain and cord that were examined (23). These results are consistent with an increase in the activity of bulbospinal serotonergic nerves in neurogenic hypertension.

Intracisternal administration of 5,6-DHT in doses that lower cord serotonin to 25-50% of control has been shown to prevent the increases in arterial blood pressure and heart rate produced by sinoaortic denervation and to reverse them when they are already established (23). This finding supports the suggestion that serotonergic bulbospinal nerves also participate in baroreceptor reflexes and help to mediate the increase in arterial blood pressure in denervation hypertension. It is interesting that, although intracisternally administered 6-OH-DA abolishes the sustained elevation of blood pressure seen after sinoaortic denervation, it does not prevent the initial increase in arterial blood pressure in the first 2 days after denervation (10). This fact is consistent with the concept of a dual control of peripheral sympathetic nerves and arterial blood pressure by bulbospinal nerves; some of these nerves are noradrenergic, but others use a different neurotransmitter such as serotonin.

The compounds used to produce selective depletion of a particular transmitter system can have appreciable nonspecific depleting effects on other monoaminergic nerves. This effect is particularly likely with pCPA (and to a lesser extent with 5,6-DHT), which may reduce catecholamine concentration in the CNS (23, 24). Some of the pressure-lowering effect of pCPA in normal animals and of 5,6-DHT in animals with neurogenic hypertension could well be nonspecific and mediated through catecholaminergic pathways. However, it is unlikely that this minor degree of depletion of central catecholamines is primarily responsible for lowering blood pressure, since it has been demonstrated that very severe depletion of spinal cord norepinephrine (to <10% of control) is required to prevent neurogenic hypertension (12). On the other hand, if regulation of arterial blood pressure depends on the balance between activity of both catecholaminergic and serotonergic nerves, minor nonspecific changes in small groups of key neurons could exert a major effect on this balance and ultimately on arterial blood pressure.

Finally, pCPA given by intraperitoneal injection may have important peripheral cardiovascular effects, although it seems likely that the effects of intracisternally administered 5,6-DHT are mediated centrally.

DEOXYCORTICOSTERONE AND SODIUM HYPERTENSION

Uninephrectomized rats treated with weekly intramuscular injections of 10 mg of deoxycorticosterone (DOCA) and given 1% saline to drink develop hypertension over a period of weeks. This model has been extensively studied by De Champlain, Axelrod, Krakoff, and Mueller, who have demonstrated in a number of studies that this form of hypertension is associated with an increase in the activity of peripheral sympathetic nerves and the adrenal medulla (13). The importance of the adrenal medulla and the sympathetic nerves in the pathogenesis of this form of hypertension has also been investigated using immunosympathectomy, intravenous administration of 6-OH-DA, and adrenalectomy (14, 15, 51-53). It seems likely that the development of hypertension in this model depends at least in part on the combined overactivity of peripheral sympathetic nerves and the adrenal medulla (14, 15).

Investigation of central catecholamine metabolism in these rats has revealed a reciprocal change in norepinephrine turnover in central neurons compared with that in peripheral neurons. There is a selective decrease in the turnover of norepinephrine.
in the medulla oblongata of DOCA-salt hypertensive rats without a change in other regions of the brain (3, 15). In the same rats, there is an increase in the turnover of norepinephrine in the heart (3). Section of the cervical spinal cord and ganglionic blockade both lower arterial blood pressure and abolish the changes in peripheral cardiac norepinephrine turnover but do not alter the decrease in the turnover of norepinephrine in the medulla (3, 15). Therefore, it has been suggested that the activity of central noradrenergic nerves normally inhibits the activity of peripheral sympathetic nerves and that in rats with DOCA-salt hypertension the reduced activity in noradrenergic neurons in the medulla oblongata is responsible for the increased activity of peripheral sympathetic nerves and hence the hypertension.

This hypothesis requires disinhibition of the peripheral sympathetic system to occur somewhere between the brainstem and the postganglionic sympathetic neuron in DOCA-salt hypertensive rats (Fig. 5). It seems possible that the elevated pressure is due to disinhibition of bulbospinal noradrenergic nerves and hence peripheral sympathetic nerves as a result of reduced activity of bulbar catecholaminergic nerves (Fig. 5). This suggestion is supported by the fact that cervical cord section abolishes both the hypertension and the increase in peripheral sympathetic activity (15) and also by the fact that intraventricular administration of 6-OH-DA prevents the induction and the development of DOCA-salt hypertension (54). It should be noted that the turnover of norepinephrine has been found to be unchanged in the whole spinal cord of DOCA-salt hypertensive rats (15), although this negative finding in the whole cord could well be masking an increase in the thoracolumbar segment, the specific region in which an increase might be expected. Furthermore, although intraventricular administration of 6-OH-DA prevents the development of DOCA-salt hypertension, it does not reverse the hypertension when it is given to rats with established DOCA-salt hypertension (7, 54). Therefore, it is possible that other transmitter systems such as bulbospinal serotonergic nerves also contribute to this model of experimental hypertension (Fig. 5). These other systems have not yet been investigated.

The reduced turnover of norepinephrine in the brainstem in this model could represent reduced activity of inhibitory noradrenergic or adrenergic nerves terminating in the vasomotor center and originating either in the NTS (Figs. 4A and 5) or elsewhere in the brainstem (Fig. 5). It could equally represent reduced activity of catecholaminergic nerves synapsing with inhibitory nerves arising from the NTS (Figs. 4B and 5). The mechanisms responsible for the changes in activity of central noradrenergic nerves in DOCA-salt hypertension have not been identified, although it has been suggested that changes in ionic concentrations of the milieu interieur might be responsible (14).

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FIGURE 5
Schematic representation of suggested disinhibition of bulbospinal monoaminergic pathways in DOCA-salt hypertension. Three alternative bulbar pathways which could each be the locus of decreased norepinephrine turnover (minuses) are indicated as CA. Decreased activity of any of these three pathways would lead to decreased inhibition of the activity of descending bulbospinal pathways which are shown as either catecholaminergic or serotonergic (5-HT) and as having an increase in activity (pluses). This decreased inhibition leads in turn to an increase in sympathetic activity (pluses). Notation is the same as that in Figure 2.
**EXPERIMENTAL RENAL HYPERTENSION**

*Catecholaminergic Nerves.*—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 (55) or by partial unilateral renal infarction with contralateral nephrectomy (56), there is an increase in the activity of peripheral sympathetic nerves to the heart and blood vessels as assessed by measurement of norepinephrine turnover using tritiated norepinephrine or synthesis inhibitors.

Peripheral immunosympathectomy will prevent the development of this form of hypertension, as will adequate chemical sympathectomy using intravenously administered 6-OH-DA (7, 53, 54). The combination of adrenalectomy and chemical sympathectomy with 6-OH-DA will prevent this form of hypertension even more successfully and will greatly attenuate it once it is established, although it will not abolish it (15, 57).

Central norepinephrine metabolism has not been studied as extensively in this model as it has been in DOCA-salt hypertension. However, it is known that there are no changes in the concentrations of endogenous norepinephrine (11, 56) or in the turnover rate of norepinephrine in the whole brain or the whole spinal cord (56). These studies are too gross to exclude significant changes in norepinephrine turnover or in the activity of catecholaminergic neurons in important regions of the brain or the spinal cord.

Destruction of central catecholaminergic nerves using injections of 6-OH-DA into the CSF has been shown to prevent completely the development of hypertension that normally follows bilateral renal wrapping in the rabbit (11) or unilateral renal artery clipping with contralateral nephrectomy (54). Intracisternally administered 6-OH-DA also causes a return of the high blood pressure to near normal levels when it is given 18 weeks after renal wrapping has resulted in chronic renal hypertension (11). Furthermore, the hypertensive response to injections of angiotensin into the lateral ventricle is markedly reduced by intracisternal administration of 6-OH-DA (11).

Thus, it seems likely that central catecholaminergic nerves play a significant role in experimental renal hypertension, although there are many gaps in our knowledge of this model. The link between the kidneys and the central catecholaminergic nerves may well lie in the action of angiotensin on catecholaminergic neurons, as reviewed previously (58). Recent experiments have shown that infusion of angiotensin into the vertebral arteries reduces the degree of inhibition of vasomotor tone induced by stimulation of baroreceptor afferents from the carotid sinus (59, 60). It is possible that central disinhibition of bulbospinal fibers may play a role in this form of hypertension too (Fig. 6).

*Serotonergic Nerves.*—Experimental renal hypertension produced by bilateral renal wrapping does not cause any significant change in endogenous levels of serotonin in the brain or the spinal cord (23), and there are no detailed studies of more dynamic aspects of central serotonin metabolism in this model. The intracisternal administration of 5,6-DHT prior to renal wrapping does not alter the

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**Diagram showing postulated disinhibition of bulbospinal monoaminergic nerves in various models of hypertension.** The minus signs represent removal of inhibition by section of baroreceptor afferents or ablation of the NTS (two forms of neurogenic hypertension) or by decreased activity of inhibitory central catecholaminergic nerves in DOCA-salt or renal hypertension. The latter inhibitory catecholaminergic nerves could be between the NTS and the VMC (Fig. 4A), or they could be quite separate to central baroreflex connections as drawn. Bulbospinal neurons are shown as catecholaminergic (CA) or serotonergic (5-HT) and as having increased activity (pluses) leading to increased sympathetic activity (pluses). Notation is the same as that in Figure 2.
rate or the degree of development of renal hypertension over a period of 8 weeks (23). When 5,6-DHT is given to rabbits with established renal hypertension, it only causes a very transient reduction in the elevated blood pressure (23). There is so far no evidence to implicate central serotonergic nerves in experimental renal hypertension.

THE SPONTANEOUSLY HYPERTENSIVE RAT

_Catecholaminergic Nerves._—The spontaneously hypertensive rat has been extensively studied with little evidence so far to implicate either the peripheral sympathoadrenal axis or the central monoaminergic neurons as primary factors in elevating the arterial blood pressure. A major problem in investigating this experimental model has been the lack of a readily available genetically matched strain of normotensive control rats. Many early suggestions concerning the role of catecholamines in the spontaneously hypertensive rat were based on comparisons with standard Wistar rats, and many have had to be revised in the light of more recent data comparing the spontaneously hypertensive rat with a variety of “control” strains, including the Kyoto Wistar rat (18, 61).

It was initially reported that there was a decrease in the activity of peripheral noradrenergic sympathetic nerves (1, 4) and an increase in the activity of the adrenal medulla, manifest in greater activity of tyrosine hydroxylase and dopamine beta-hydroxylase (62). It is now clear from a study in nine strains of rats that the changes in the adrenal biosynthetic enzymes are not specific to the spontaneously hypertensive rat and occur in other normotensive strains in relation to genetic variation which has no effect on the level of blood pressure (61). It should be noted that intravenously administered 6-OH-DA does not prevent or abort the hypertension in this model (63).

Early studies also suggested a decrease in the activity of catecholaminergic neurons in the brainstem of the spontaneously hypertensive rat (1, 2). This decrease was not confirmed (4) and has since been shown not to be related to the level of arterial blood pressure but rather to the result of genetic variation in catecholamine synthesis in the brainstem of the spontaneously hypertensive rat and in a multitude of control normotensive strains of rats (18, 61). However, injection of 6-OH-DA into the lateral ventricle of the spontaneously hypertensive rat before the development of hypertension has been shown to prevent the progressive elevation of arterial blood pressure (54). Since intraventricular administration of 6-OH-DA to the mature spontaneously hypertensive rat with established hypertension only causes a transient fall in blood pressure (8), it has been suggested that central noradrenergic neurons may be involved in initiating or triggering the hypertension in the developing spontaneously hypertensive rat but that they do not play a significant role in maintaining the elevated blood pressure (7, 8).

One interesting recent report concerns the possible role of the endogenous brain isorenin-angiotensin system (64, 65). It has been observed that levels of angiotensin II are high in the CSF of the spontaneously hypertensive rat and that administration of specific angiotensin antagonists into the CSF lowers the arterial blood pressure in the spontaneously hypertensive rat but not in control animals (66). In view of the well-documented interrelationships between angiotensin and catecholaminergic mechanisms, it seems possible that the high blood pressure in the spontaneously hypertensive rat could depend on central pressor actions of angiotensin (either renal or central in origin) mediated through actions on central catecholaminergic nerves.

_Serotonergic Nerves._—In the only study of the role of serotonin in this model, it has been found that chronic daily oral administration of pCPA reduces systolic blood pressure (44). This finding raises the possibility that central serotonergic nerves are involved in the pathogenesis of the high blood pressure in the spontaneously hypertensive rat, although findings with orally administered pCPA could also conceivably be due to peripheral effects.

CONCLUSIONS

There are definite qualitative and quantitative differences in the activity of central monoaminergic nerves in these models of experimental hypertension and in normal animals. These differences are manifest in the markedly different patterns of central monoamine metabolism and the different central effects of selective antagonists on arterial blood pressure in the various preparations. It is clearly not tenable to regard all of these central circulatory effects as nonspecific sequelae of interference with central aminergic tracts participating normally in the normal control of arterial blood pressure.

Central catecholaminergic nerves play an important role in the regulation of arterial blood pressure. Although they appear to have little importance in the maintenance of resting arterial blood pressure in normal unstressed animals, they play a
major role in the reflex control of blood pressure through the arterial baroreceptor reflexes. The activity of bulbospinal noradrenergic nerves appears to facilitate the increase in arterial blood pressure in neurogenic hypertension and possibly in DOCA-salt hypertension. The activity of brainstem catecholaminergic nerves appears to inhibit the activity of bulbospinal noradrenergic and serotonergic nerves and hence to have a depressor effect on arterial blood pressure (Fig. 6). Disinhibition of bulbospinal noradrenergic and serotonergic fibers by deafferentation of arterial baroreceptors (neurogenic hypertension) or by decreased activity of inhibitory catecholaminergic nerves in the brainstem (DOCA-salt and renal hypertension) could play a significant role in the pathogenesis of experimental hypertension (Fig. 6). The participation of central catecholaminergic nerves in genetic hypertension (the spontaneously hypertensive rat) has not yet been established.

Central serotonergic nerves also appear to play a significant role in the regulation of arterial blood pressure in normal animals and in some models of experimental hypertension. The activity of bulbospinal serotonergic nerves seems to facilitate the maintenance of arterial blood pressure in normal animals and the increase in blood pressure in experimental neurogenic hypertension, although this matter is still controversial. Central serotonergic nerves do not appear to contribute to experimental renal hypertension, but they may play a role in elevating the pressure in the spontaneously hypertensive rat.

The central connections of the autonomic nervous system utilize a variety of neurotransmitters in much the same way as do the peripheral components. It should be expected that each of these central neurotransmitters can be facilitatory or inhibitory in different pathways and that each can synapse with a variety of functionally distinct receptors. These facts, together with the presence of short excitatory or inhibitory interneurons, increase the complexity of experimental data on the functional role of central monoaminergic pathways.

References

8. HAUSLER G, GEROLD M, THOREN T: Cardiovascular effects of 6-hydroxydopamine injected into a lateral brain ventricle of the rat. Naunyn Schmiedebers Arch Pharmacol 274:211-228, 1972
17. DOBA N, REIS DJ: Role of central and peripheral adrenergic mechanisms in neurogenic hypertension produced by brainstem lesion in rats. Circ Res 34:293-301, 1974

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42. Lewis PJ, Rawlings MD, Reid JL: Acute thermoregulatory and cardiovascular effects of 6-hydroxydopamine administered centrally in rabbits and cats (abstr). Br J Pharmacol 44:559p, 1972
43. Kornner PI, White SW: Circulatory control in hypoxia by the sympathetic nerves and adrenal medulla. J Physiol (Lond) 184:272-290, 1966
57. Grewal RS, Kaull CL: Importance of sympathetic nervous
Brain amines and models of experimental hypertension.
J P Chalmers

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