THE CENTRAL NEURAL REGULATION BY BARORECEPTORS OF PERIPHERAL CATECHOLAMINERGIC MECHANISMS

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THE REFLEXES from baroreceptors play an important role in governing the discharge of sympathetic neurons to blood vessels. As such, they serve two principal functions. First they are of importance in the reflex regulation of the circulation. Second, since the activity of the sympathetic innervation of the vasculature is a major source of catecholamines (SPECTOR, 1972) and since the rate of synthesis, the activities and possibly quantities of synthetic enzymes, and the rate of release of catecholamines varies directly with the intensity of nerve impulse activity (PLETSCHER, 1972), the baroreceptors probably help regulate much of the catecholamine metabolism in the body.

The baroreceptors, under normal circumstances, are tonically active (KORNER, 1971) thereby exerting a continuous inhibition on the discharge of sympathetic nerves. Withdrawal of baroreceptor input, either by reduced stretch of the vascular receptors [most commonly initiated by assumption of an upright posture (GAUER and THRON, 1965)] or by transection of afferent nerves, results in a differentiated release of preganglionic sympathetic fibres from inhibition. The major cardiovascular response to peripheral deafferentation of baroreceptors is arterial hypertension (KORNER, 1965; KRIEGER, 1967; DE QUATTRO *et al.*, 1969).

The magnitude of the total inhibition of sympathetic nerve activity exerted by baroreceptors has previously never been determined. Denervation of baroreceptors of the carotid sinus and aortic arch region by transection of the carotid sinus and aortic depressor nerves (sino-aortic denervation) is not sufficient to interrupt afferent activity from baroreceptors of other major arteries or of stretch receptors of the heart and the lesser circulation which are carried in the vagus (PAINTAL, 1969). The hypertension produced by sino-aortic denervation is only moderate (KORNER, 1965; KRIEGER, 1967; DE QUATTRO *et al.*, 1969).

We have recently sought to determine in a new way just how much inhibition is exerted by baroreceptors on the sympathetic neural drive to the circulation. We have done this by denervating baroreceptors *centrally* rather than peripherally. This has been accomplished by placing small electrolytic lesions bilaterally in a major site of termination of baroreceptors in the brain, the area of the *nucleus tractus solitarii* (NTS) located at the obex (MIURA and REIS, 1969; MIURA and REIS, 1972). Lesions at this site will destroy not only primary afferent fibres but also first order neurons and will abolish all depressor responses elicited from vascular stretch receptors in arteries and the heart (LEE *et al.*, 1972; MIURA and REIS, 1972).

The effects of such lesions in the unanaesthetised rat are profound (DOBA and

REIS, 1973). Following the placement of such lesions and immediately upon awakening from anaesthesia the animals develop an elevation of systolic, diastolic, and mean arterial blood pressures to about 160 per cent of control without changes in heart rate. The elevation of blood pressure is entirely attributable to the 2·5-fold increase in the total peripheral resistance. The elevated resistance produces an overload of the left ventricle with consequent reduction of stroke volume, and an increase in end-diastolic pressure resulting in a fall of cardiac output to 60 per cent of normal. This ultimately leads to failure of the left ventricle and by 4–6 hr after placing the lesion the animals develop acute pulmonary oedema and die.

The hypertension is not due to changes in blood gases nor the release of pressor substances from kidneys or adrenal glands since prior adreno-nephrectomy does not reduce the magnitude of the hypertension. However, the hypertension appears to depend on the integrity of as yet unknown regions of the upper brainstem and the forebrain since the hypertension, once established, is abolished by mid-collicular decerebration. It probably is mediated by ascending polysynaptic pathways (MIURA and REIS, 1969) since it is extremely sensitive to anaesthetics.

All present evidence suggests that the hypertension is neurogenic, is due to differentiated activation of sympathetic neurons, and is mediated by alpha-adrenergic receptors. First, the hypertension can be abolished by ganglionic blocking agents or by the alpha-adrenergic blocking agent, phentolamine. Second, treatment of rats with 6-hydroxydopamine (6-OHDA) will also block the experimental hypertension produced by NTS lesions but only after the adrenal glands have been removed (Fig. 1). This finding, paralleling the recent observations by DE CHAMPLAIN and VAN AMERINGEN (1972), in animals with DOCA-salt hypertension indicates that adreno-medullary secretion is increased following a lesion of the NTS, and in the absence of sympathetic fibers the amount of adrenal catecholamines released is sufficient to maintain blood pressure. The observation also implies that adreno-medullary secretion is tonically inhibited by baroreceptors. Indeed, that the release of adrenal catecholamines may be suppressed by baroreceptor activity is also indirectly suggested by the experiments of DE QUATTRO *et al.*, (1969), who have demonstrated that chronic denervation of sinoaortic nerves in rabbit produces a trans-synaptically mediated increase in the activities of adrenal tyrosine hydroxylase and PNMT.

Some recent findings suggest that the profound and sustained increase of the release of catecholamines from sympathetic neurons resulting from central baroreceptor deafferentation may have some effects on receptor mechanisms within the blood vessels themselves. AMER (1973), has found that the levels of cyclic AMP in the aorta of spontaneously hypertensive rats and rats made hypertensive by prolonged stress may be significantly reduced. The reduction is due to an increase in degradation of cyclic AMP by enhanced activity of the high affinity phosphodiesterase (PDE II). The reduction of cyclic AMP has been considered as a possible mechanism whereby arterial resistance is increased since a reduction of the cyclic nucleotide in smooth muscle is generally associated with increased contractility (SOBEL and MAYER, 1973). In the artery this may also reflect a decreased sensitivity of the beta receptor.

A similar reduction in cyclic AMP in aorta and also in the heart can be found in rats made hypertensive by NTS lesions within 90 min after placement of NTS lesions

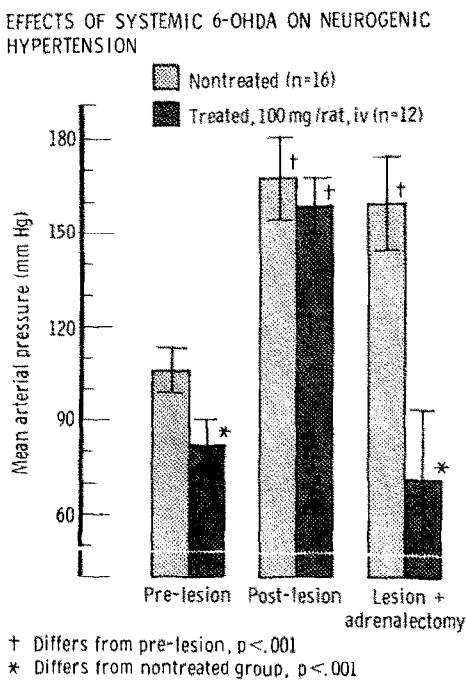

FIG. 1.—Effects of systemic 6-hydroxydopamine (6-OHDA) on neurogenic hypertension in rat. 6-OHDA was administered i.v. (100 mg/rat) in 0·5 ml of ascorbic acid vehicle 24 hr prior to surgery. Under halothane anaesthesia a cannula was inserted into the tail artery in treated and untreated groups. Anaesthesia was discontinued and basal blood pressure (BP) measured. Animals were reanaesthetised, lesions placed in NTS (DOBA and REIS, 1973) and anaesthesia discounted. Ninety minutes later BP was measured, the animals reanaesthetized and adrenals removed. BP was again measured after recovery from anaesthesia. In separate experiments this dose of 6-OHDA produced a 70–80 per cent fall ($P < 001$) in NE in heart and spleen but not in brainstem.

(Table 1). As in other models for hypertension the fall of cyclic AMP is associated with an increase in the activity of the high affinity phosphodiesterase system without a change in the basal activity of adenylate cyclase. Paralleling the fall of cyclic AMP there is an elevation of cyclic GMP in the aorta. This may reflect in some manner activation of alpha-adrenergic receptors by norepinephrine.

These changes in the metabolism of cyclic nucleotides in acute neurogenic hypertension taken with the previous studies (AMER, 1973) suggest that intense activation of sympathetic neurons to blood vessels can lead to an activation of the phosphodiesterase system resulting in a reduction of the cyclic nucleotide AMP, an increase in GMP, a reduced availability of beta-adrenergic mechanisms, and a resultant vasoconstriction. Whether this may represent a mechanism of presynaptic control of postsynaptic vascular reactivity by the baroreceptors is a fascinating question for future research.

While baroreceptor reflex mechanisms in the brain appear to play a role in modulating peripheral catecholamine release, metabolism and possibly the catecholamine receptors themselves, the excitability of the baroreceptor reflex is itself controlled by other brain regions including forebrain, hypothalamus and cerebellum

TABLE 1. CHANGES IN CYCLIC NUCLEOTIDES AND ASSOCIATED ENZYMES IN AORTAS OF RATS WITH ACUTE NEUROGENIC HYPERTENSION

	Sham	*Lesion*
Cyclic AMP[a]	0·76 ± 0·11 (4)	0·43 ± 0·01 (5)†
Cyclic GMP[a]	0·07 ± 0·01 (5)	0·12 ± 0·02 (5)*
Adenylyl cyclase[b]	24·7 ± 3·00 (5)	19·2 ± 5·10 (5)‡
Guanylyl cylase[c]	3·78 ± 0·76 (4)	4·15 ± 0·45 (4)‡
Phosphodiesterase (PDE) Activity[d]		
Cyclic AMP as substrate		
High Substrate (PDE I)	20·0 ± 2 (7)	20·0 ± 2 (7)
Low Substrate (PDE II)	0·04 ± 0·01 (7)	0·06 ± 0·004 (6)†
Cyclic GMP as substrate		
High Substrate (PDE I)	20·0 ± 4 (6)	20·0 ± 2 (6)‡
Low Substrate (PDE II)	0·14 ± 0·02 (6)	0·33 ± 0·02 (7)†
Blood pressure (mm Hg)	122 ± 2·1 (7)	173 ± 6·9 (7)†

Each value represents mean ± S.E.M. (n) = number of animals
(a) pm/mg wet tissue
(b) nmoles cyclic AMP formed/10 mg wet tissue/10 min
(c) nmoles cyclic GMP formed/10 mg wet tissue/20 min
(d) nmoles cyclic nucleotide hydrolysed/5 mg wet tissue/10 min at 30°C.
* $P < 0.05$
† $P < 0.01$
‡ not significant.

Bilateral lesions were placed in NTS with animals anaesthetised with halothane (3%). Blood pressure was recorded from the tail artery. Immediately after lesions the anaesthesia was discontinued. The animals were killed 90 min later and aortas removed and frozen in liquid N_2. Sham controls had electrodes inserted into NTS but no lesions were made. The results obtained in sham animals did not differ from unoperated controls. The method for assay of cyclic AMP, adenylyl cyclase and phosphodiesterase were as described by AMER (1973). Phosphodiesterase activity was determined at two substrate concentrations (0.8×10^{6} and 0.5×10^{-3} M, cyclic AMP; 1×10^{-6} and 0.5×10^{-3} M, cyclic GMP). Cyclic GMP was isolated in 4N formic acid fraction eluted from Dowex-1-formate columns as described by MURAD *et al.* (1971), and assayed by the method of MURAD and GILMAN (1971). Guanylyl cyclase was assayed by a method similar to that used for adenylyl cyclase except that GTP was substituted for ATP and Mn^{2+} was substituted for Mg^{2+}.

(MORUZZI, 1940; REIS and CUENOD, 1965; GEBBER and SNYDER, 1970). Moreover some of the control may be by those neurons which synthesise, store and release the neurotransmitter NE.

The evidence for this is two-fold. First CHALMERS and REID (1972), have recently shown that the hypertension produced in rabbit by sino-aortic denervation can be aborted or abolished by the intra-cisternal injection of the adrenolytic agent 6-OHDA in doses which do not alter the content of catecholamine peripherally, but will significantly reduce them within the CNS. Second, we have recently found that the hypertension produced in rats by NTS lesions may similarly be affected by intra-cisternal administration of 6-OHDA. The intra-cisternal injection of 600 μg/rat of 6-OHDA, while not affecting the mean blood pressure, will significantly attenuate the hypertension produced by NTS lesions (Fig. 2) confirming Chalmers' and Reid's observations in rabbit. This effect is dose-related. In rat the effects of intra-cisternal 6-OHDA on the hypertension produced by NTS lesions can only be attributed to effects on central catecholamines since it does not alter the concentrations

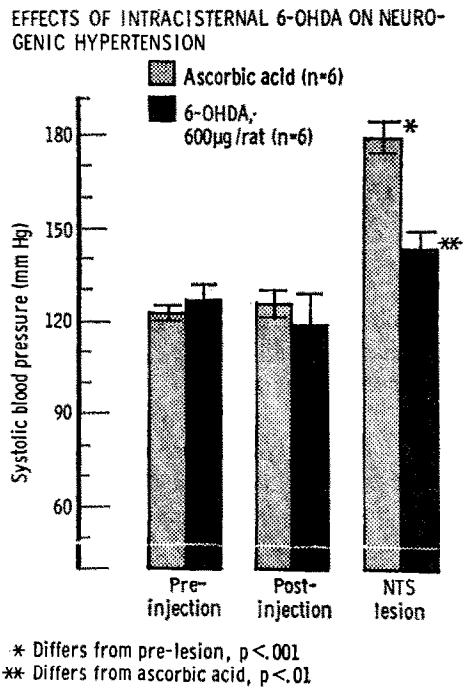

FIG. 2.—Effects of intracisternal 6-OHDA on neurogenic hypertension in rat. 600 μg of 6-OHDA in 6 μl of ascorbic acid vehicle or vehicle alone was administered intracisternally and blood pressure measured daily by a tail cuff method. Three days later animals were anaesthetised with halothane, lesions placed in NTS (DOBA and REIS, 1973) and blood pressure measured 90 min later. In separate experiments such treatment resulted in a 35 per cent ($P < 0{\cdot}01$) fall of NE in spinal cord but not in brainstem, hypothalamus or cerebellum.

of catecholamines in peripheral adrenergic endings nor will this dose when administered intravenously in the animal with adrenal glands intact in any way attenuate the hypertension. On the assumption that the hypertension produced by NTS lesions is a consequence of central deafferentation of baroreceptors, the evidence strongly suggests, in agreement with CHALMERS and REID (1972), that central catecholaminergic neurons are involved in mediating the hypertension resulting from withdrowal of the inhibition of preganglionic sympathetic neurons by baroreceptors. Moreover they are inhibitory, directly or indirectly, to the discharge of preganglionic neurons in the spinal cord.

The site at which the adrenergic terminals act and the location of the cell bodies giving rise to these terminals is not known. It does not seem likely that all central catecholamine systems are involved. For example, the local injection of 6-hydroxydopamine into the lateral hypothalamus in doses sufficient to impair catecholamine levels within the hypothalamus and forebrain (SMITH *et al.*, 1972) does not attenuate the hypertension. However, when 6-OHDA was administered intracisternally in a dose sufficient to abort NTS hypertension (Fig. 2) the only area showing a reduction in NE was the spinal cord. We would therefore agree with CHALMERS and REID (1972), that it is more likely that the effects of NE are mediated via a descending NE system which in some manner is inhibitory for the expression of sympathetic activity at the level of the spinal cord.

This brief review has only touched on one neural system involved in the mediation of reflex drive to catecholamines in the periphery. Other central systems also participate in the regulation of sympathetic tone. For example, we have recently discovered the presence of regions of the pons and upper medulla distinct from the NTS from which a marked elevation of blood pressure can be evoked by local distortion (HOFF and REIS, 1970; DOBA and REIS, 1972a). These regions which probably mediate the so-called Cushing reflex (i.e. the increase of blood pressure in response to an increase of intracranial pressure) may be another determinant of sympathetic nerve activity possibly by driving the vasomotor neurons tonically. The orthostatic reflexes are modulated not only by baroreceptors but also probably from the vestibular apparatus and cerebellum as well (DOBA and REIS, 1972b, c, d). Finally, there are the important pathways descending from higher regions which appear to be the link between behaviour and the circulation coupling appropriate changes of the activity of the sympathetic nervous system to complex behavioural patterns such as fighting, feeding and exercise (REIS, 1972). These too undoubtedly contribute to the regulation of catecholamine metabolism in the body. Thus, the central nervous system integrating reflexes acting on the circulation initiated from the periphery and those associated with behaviour originating in the brain must play an essential role in the regulation of systemic catecholamines.

SUMMARY

The activity of preganglionic sympathetic neurons to blood vessels are tonically inhibited by baroreceptors. Removal of this inhibition by central deafferentation produced by lesions at a site of baroreceptor termination in the brainstem results in a marked and differentiated increase in sympathetic nerve activity resulting in neurogenic hypertension, alteration of cyclic nucleotide metabolism in the aorta and secretion of adrenal medullary catecholamines. Central baroreceptor mechanisms, themselves modulated by noradrenergic neurons, serve to regulate the release and metabolism of peripheral catecholamines and possibly their receptors.

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