ROLE OF SYMPATHETIC FIBRES AND OF ADRENAL MEDULLA IN THE MAINTENANCE OF CARDIO-VASCULAR HOMEOSTASIS IN NORMOTENSIVE AND HYPERTENSIVE RATS

JACQUES DE CHAMPLAIN* and MARIE-REINE VAN AMERINGEN
Centre de Recherches en Sciences Neurologiques, Département de Physiologie,
Faculté de Médecine, Université de Montréal, Montréal, Canada

THE CONCEPT of modulation of cardiovascular system by the autonomic nervous system has been accepted for a long time. However, the efferent sympathetic component of the autonomic nervous system is more dynamically related to the peripheral cardiovascular system by a dense plexus of excitatory fibres distributed to the heart and to all vascular beds. Small arterioles which are crucial to the homeostasis of arterial blood pressure were found to be the most densely innervated segments of the vascular tree (NORBERG, 1967). In addition to this network of excitatory fibres, the sympathetic nervous system is also responsible for the control of catecholamine secretion by the adrenal medulla which can also influence the heart and blood vessels by acting on specific receptors to catecholamines localized in these structures.

Little is known about the relative contribution of each component of the sympathetic system in the maintenance of normal cardiovascular functions. In numerous previous studies, the effects of sympathectomy were studied after surgical denervation, after treatment with nerve growth factor antiserum or after administration of catecholamine depleting drugs such as reserpine. Most of these techniques however were either non specific to the peripheral fibres or, resulted in an incomplete sympathectomy so that the conclusions reached with these procedures may be questionable.

The discovery that 6-hydroxydopamine (6-OH-DA) could specifically and selectively destroy adrenergic nerve fibres (TRANZER and THOENEN, 1967) has given a more specific and more useful tool for the study of the role of the sympathetic nervous fibres. In periphery, 6-OH-DA when given in sufficient amount, causes the degeneration of the great majority of sympathetic fibres without destroying the ganglion cell bodies or the adrenal medulla.

NORMOTENSIVE RATS

In normotensive rats and dogs, the intravenous administration of 6-OH-DA is immediately followed by a marked and prolonged sympathomimetic effect characterized by an increase of blood pressure and heart rate due to the massive release of norepinephrine from the nerve endings occurring during the acute phase of degeneration (DE CHAMPLAIN and VAN AMERINGEN, 1972; GAUTHIER *et al.*, 1972). In the following hours and days, the blood pressure stabilizes about 30 mm Hg lower and the heart rate is slightly reduced (Fig. 1, Table 1). On the other hand, bilateral adrenalectomy alone causes only a slight insignificant decrease in blood pressure of

* Member of the Medical Research Council Group in Neurological Sciences at the Université de Montréal.

about 10 mm Hg and no change in the heart rate. It therefore appears from these results that the sympathetic nervous fibres are more dynamically related to the maintenance of blood pressure and heart rate than the adrenal medulla. Nevertheless, after the removal of either component of the sympathetic system, the animals appeared relatively normal and could easily survive. The combination of both procedures produced more dramatic changes than expected from the addition of either individual effects. After chemical sympathectomy, bilateral adrenalectomy caused a rapid fall in blood pressure and heart rate of more than 40 mm Hg and 100 beats/min respectively (Fig. 1, Table 1). In the hours following adrenalectomy the blood pressure stabilized around 50 mm Hg and the animals remained in a state of shock until death which occurred in all cases within 2–3 hr.

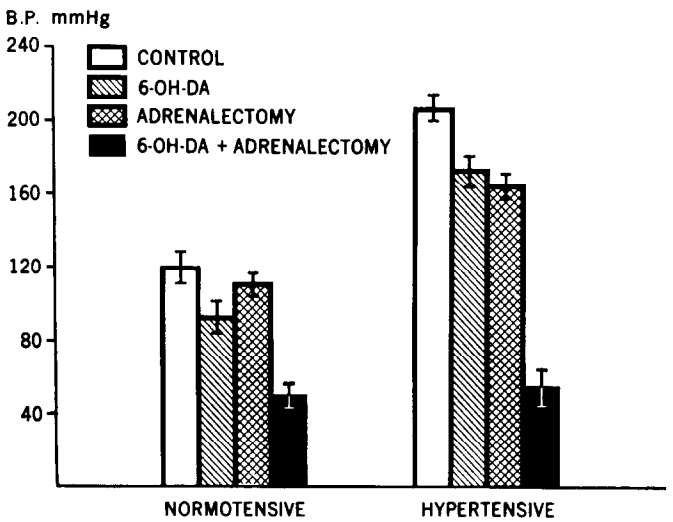

FIG. 1.—Systolic arterial pressure (mm Hg) in unanaesthetized normotensive and (DOCA and saline) hypertensive rats 8 days after one intravenous injection of 6-OH-DA (100 mg/kg) or bilateral adrenalectomy. The black bars represent the blood pressure values 60 min after adrenalectomy in animals previously sympathectomised with 6-OH-DA. These latter values were recorded under anaesthesia. Each bar represents the mean ± S.E. of 4–8 animals.

TABLE 1. EFFECT OF 6-OH-DA AND/OR BILATERAL ADRENALECTOMY ON THE HEART RATE (BEATS/MIN) OF ANAESTHETIZED NORMOTENSIVE AND (DOCA AND SALINE) HYPERTENSIVE RATS

	Normotensive	Hypertensive
Control	283 ± 22	245 ± 12
6-OH-DA	255 ± 29	228 ± 44
Adrenalectomy	285 ± 32	238 ± 25
6-OH-DA + adrenalectomy	184 ± 11*	182 ± 28

The values represented in this table are those observed 18 hr after one intravenous injection of 100 mg/kg of 6-OH-DA or 60 min after adrenalectomy. Each number is the mean ± S.E. of 4–6 rats.

* $P < 0.01$ vs control values.

These findings strongly suggest that after the removal of sympathetic fibres, the adrenal medulla has the capacity to increase its activity and substitute partially the function of sympathetic nervous fibres in maintaining blood pressure and heart rate. The acute and marked effects of adrenal clamping or adrenalectomy in sympathectomised animals are most probably the result of the interruption of catecholamine secretion by the adrenal medulla. The effects observed occur too rapidly to be attributed to the adrenocortical steroids and moreover, similar effects were also observed in animals which were given cortisone replacement therapy. In addition, identical fall in blood pressure could also be observed in sympathectomised rats after treatment with an alpha blocker. The compensatory role of the adrenal medulla is also supported by the study of MUELLER *et al.* (1969), who reported that the synthesis of catecholamine by the adrenal medulla was doubled in sympathectomised rats forty hours after the injection of 6-hydroxydopamine.

It appears that the sympathetic fibres may also have the capacity to compensate in the absence of the adrenal medulla. In the hours following bilateral adrenalectomy, a marked increase in the norepinephrine turnover could be observed in peripheral sympathetic nerve fibres (DE CHAMPLAIN and VAN AMERINGEN, 1972; LANDSBERG and AXELROD, 1968). It is therefore possible to postulate that a functional balance exists between the activity of either component of the sympathetic system in the regulation of the heart rate and blood pressure in normotensive animals. This functional relationship is probably determined partly through baroreceptor reflexes and partly through circulating catecholamine levels.

The present observations were made under acute conditions and it is not excluded that other more chronic compensatory mechanisms could develop and eventually contribute to the maintenance of cardiovascular functions following the chemical sympathectomy. It is likely that the development of a supersensitivity to catecholamines, the change in blood volume and the activation of the renin-angiotensin system could contribute to the cardiovascular homeostasis in chronically sympathectomised animals.

HYPERTENSIVE ANIMALS

It is known that the regulation of blood pressure involves the interaction of various systems and factors. An elevation of blood pressure could result from a variety of dysfunctions occurring at any point in this regulatory mechanism. Several systems and factors have been suspected to participate in the physiopathology of hypertension and it seems difficult, at this point, to consider exclusively only one given factor or system as the basic mechanism of hypertension. Hypertensive disorders result most probably from a variety of dysfunctions many of which we are still unable to recognize. For these reasons, it is risky to recognize only one experimental model for human hypertension. Several models have been developed in various animal species and it is likely that each one illustrates different facets of the human disease. We have more specifically studied the role of sympathetic fibres and adrenal medulla in two experimental models of hypertension using an approach similar to that used in normotensive animals.

In previous studies made in collaboration with Krakoff, Mueller and Axelrod on one experimental model produced by the administration of desoxycorticosterone (DOCA 10 mg/week) and saline (1 % drinking solution), we were able to demonstrate

that the turnover of norepinephrine was markedly increased in the sympathetic fibres of various peripheral vascular organs (DE CHAMPLAIN, 1972). Studies on the subcellular distribution of norepinephrine and on the pattern of metabolites suggested that there are greater quantities of norepinephrine available at the receptor sites in this condition. In addition, it was also found that the blood pressure levels varied in relation to the sodium intake in parallel with the variations in peripheral sympathetic activity thus suggesting that sodium or other related ions might be a determinant factor in the modulation of sympathetic activity (DE CHAMPLAIN *et al.*, 1969).

Chemical sympathectomy and adrenalectomy alone produced greater changes in blood pressure in DOCA and sodium hypertensive animals that in normotensive animals (Fig. 1). After either one of these procedures the blood pressure was lowered by about 40 mm Hg thus suggesting a more active contribution of both components of the sympathetic system in the maintenance of blood pressure in this group of animals than in normotensive rats. Nevertheless, after the removal of either component of the sympathetic system, the blood pressure remained at hypertensive levels. When the adrenal glands were removed in 6-OH-DA treated hypertensive rats, the blood pressure fell rapidly and markedly by more than 70 mm Hg thus indicating that the adrenal medulla had the capacity to compensate the loss of sympathetic fibres in these animals as well. It is also interesting to note that after adrenalectomy and sympathectomy, the basal blood pressure and heart rate reached in DOCA and sodium hypertensive animals were identical to those found in normotensive animals after the same procedures (Fig. 1, Table 1). This observation strongly suggests that the most likely factor which could account for an elevated blood pressure in rats treated with DOCA and sodium is a synergic hyperactivity of both the sympathetic fibres and the adrenal medulla.

Since both components of the sympathetic system appear to be hyperactive in this form of hypertension it is possible that this might be the result of a dysfunction at the site of the pressure regulatory centres. In support of that hypothesis, a marked decrease in the norepinephrine turnover rate was found in the brain stem of DOCA hypertensive animals whereas the turnover rates were found unchanged in the telediencephalon and spinal cord (VAN AMERINGEN, M. R., and DE CHAMPLAIN, J., unpublished observations). This decrease in the norepinephrine turnover does not seem to be a consequence of the elevation of blood pressure since it was still present in DOCA and saline treated rats in which blood pressure was restored to normotensive levels following a cervical spinal cord section.

The same protocol was also used to investigate the role of the sympathetic system in another model of experimental hypertension induced by stenosis of one renal artery and contralateral nephrectomy. Although, an hyperactivity of the renin-angiotensin system has been associated with this form of hypertension (GROSS *et al.*, 1965), there are several indications that the sympathetic system might be involved at some stages in the physiopathology of hypertension in that model (DE CHAMPLAIN, 1972). Although adrenalectomy did not produce any significant change, chemical sympathectomy by 6-OH-DA produced a greater fall in blood pressure and heart rate than in normotensive and in DOCA hypertensive rats (Fig. 2). However, after the removal of both components of the sympathetic fibres, the residual blood pressure was considerably higher than normotensive and DOCA hypertensive rats thus suggesting an additional pressor mechanism in that form of hypertension. The removal of the

clamped kidney in sympathectomised and adrenalectomised animals lowered the blood pressure rapidly to the same residual blood pressure than in normotensive and DOCA hypertensive animals after removal of both components of the sympathetic system. Thus, both the sympathetic nervous fibres and the renal pressor system appear to participate in the maintenance of an elevated blood pressure in renal hypertension.

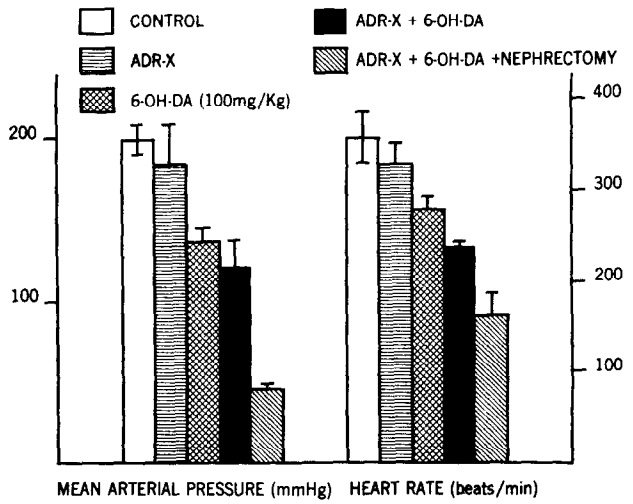

FIG. 2.—Cardiovascular effects of chemical sympathectomy (6-OH-DA 100 mg/kg), bilateral adrenalectomy (ADR-X), or both, with and without nephrectomy in rats made hypertensive by renal artery stenosis and contralateral nephrectomy 45 days previously. The values were recorded under anaesthesia and observed 18 hr after one intravenous injection of 6-OH-DA (100 mg/kg), 60 min after adrenalectomy and 120 min after total nephrectomy. Each bar is the mean ± S.E. of 3 animals.

CONCLUSION

In normotensive animals it seems that the sympathetic nervous system (the sympathetic fibres and the adrenal medulla) is essential for the maintenance of cardiovascular functions. It is difficult at this point to determine whether the sympathetic nervous system plays a primary role in the pathogenesis of certain forms of human and experimental hypertension or whether it contributes only to certain stages of the hypertensive disease. It is likely that both possibilities exist. In the two models of experimental hypertension which were studied, an hyperactivity of the sympathetic system could be observed. In DOCA and sodium hypertensive animals it appears that an activation of the whole sympathetic system is the main factor responsible for an elevation of blood pressure, whereas, in renal hypertensive rats, an activation of the renin-angiotensin system is associated with an hyperactivity of the sympathetic fibres. It is hoped that the development of more sensitive and sophisticated means of investigation in coming years will permit a better understanding of the functioning of the sympathetic nervous system in the physiopathology of various human hypertensive diseases so that a more rational therapy could be developed for these diseases.

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