Neural and non-neural mechanisms in spontaneous hypertension

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Summary

1. The pathogenesis of hypertension in spontaneously hypertensive rats (SHR) is considered to consist of neurogenic and non-neurogenic factors, both of which contribute to initiation and maintenance mechanisms.

2. Neurogenic factors have been demonstrated by the destruction of the central nervous system, sympathectomy, recording of sympathetic discharge, hind-limb perfusion and study of noradrenaline. These factors are mainly involved in the initiation of hypertension, and they appear to diminish in importance after the establishment of hypertension, as indicated by the noradrenaline-turnover study.

3. The non-neurogenic factors have been demonstrated haemodynamically by increased peripheral vascular resistance remaining even after sympathectomy. They have also been demonstrated histologically by the narrowing of resistance arteries with medial hyperplasia or hypertrophy. These factors appear to participate in maintenance mechanisms.

4. Increased incorporation of labelled amino acid into non-collagenous and collagenous protein of the arterial walls precedes medial hypertrophy and hypertensive arteriosclerosis. It seems to play a role therefore both during neurogenic initiation and later non-neurogenic maintenance of blood pressure.

5. Non-collagenous protein metabolism of arterial walls is increased in young SHR, and it is partly dependent on neural innervation as detected by surgical or pharmacological sympathectomy. It indicates a close linkage between neurological and structural changes in the initiation of spontaneous hypertension.

Key words: amino acid incorporation, collagenous protein, hypertension, neurogenic factors, non-collagenous protein, noradrenaline turnover, peripheral vascular resistance, sympathectomy.

Introduction

Spontaneously hypertensive rats (Okamoto & Aoki, 1963), now in the F35 generation in our Department, are regarded as the best animal model for essential hypertension. All rats of this strain develop primary hypertension without any organic lesions, with an initial increase in peripheral resistance and later hypertensive lesions similar to those in man (Okamoto, 1972). This hypertension is multifactorially inherited through a small number of major genes and modified by environmental factors such as stress and salt intake (Yamori & Okamoto, 1974). Although hypertensive mechanisms are not yet completely clarified, our studies up to the present indicate the importance of neurogenic factors in the initiation mechanisms of spontaneous hypertension. They also show subsequent involvement of non-neurogenic factors in its maintenance.

Methods

(1) Neurogenic factors were evaluated by the destruction of the central nervous system, the recording of sympathetic discharge (Okamoto, Nosaka, Yamori & Matsumoto, 1967), the effect of sympathectomy, perfusion experiments (Nosaka, Yamori, Ohta & Okamoto, 1972) and by noradrenaline-turnover studies (Yamori, 1974).

(2) Non-neurogenic vascular factors were studied histometrically (Kyogoku, Haebara, Ooshima, Yamori, Ikehara, Ohta, Okuda & Okamoto, 1972;
Yamori & Sasagawa, 1975) and the metabolic base for structural vascular alteration was studied by the quantitative estimation of proline incorporation into the vascular walls of rats, which were killed 4 h after infusion of labelled proline (Yamori, 1974, 1975).

(3) The relationship between the neural activity and the vascular protein synthesis was studied in pre-hypertensive SHR (1). The effect of denervation on vascular protein synthesis was assessed by labelled lysine incorporation into non-collagenous protein of the mesenteric arteries (Yamori, Nakada & Lovenberg, 1976).

Results

Neurogenic initiation of hypertension

This was shown in SHR by the following experimental studies. Complete splanchnicotomy with mesenteric artery denervation effectively arrested the development of spontaneous hypertension in young SHR (Yamori et al., 1976), although splanchnicotony was not so effective in adult SHR. Hind-limb perfusion (Nosaka et al., 1972) showed that the high initial perfusion pressure in SHR 3 months old greatly decreased after denervation, but the pressure still remained higher than in control rats. Noradrenaline infusion elicited a greater increase in perfusion pressure, but the amount of noradrenaline required to compensate for the initial fall was greater in SHR than in control rats. These observations indicate that greater vascular resistance in SHR is dependent on the neural component and partly on increased vascular reactivity. It may also be dependent on structural vascular change (Folkow, Hallbäck, Lundgren, Sivertson & Weiss, 1973).

Moreover, cardiac noradrenaline turnover, which may reflect sympathetic activity, increased in SHR in the pre-and early hypertensive stages, that is, 30 and 60 days after birth. But it was no longer elevated at 100 days when hypertension was stabilized (Yamori, 1974). These findings suggest that neurogenic mechanisms are very active only in the early stage of hypertension, but are soon replaced by non-neurogenic mechanisms.

Participation of vascular factors

This was indicated by our histometrical studies. Hypertrophy or hyperplasia in resistance arteries as well as in the aorta was already noted in the relatively early stage of hypertension (Kyogoku et al., 1972). Also vascular wall alterations, such as thickness of the aortic wall and hyperplasia of the media, were detected in SHR 4 months old (Yamori & Sasagawa, 1975).

Before these structural changes metabolic changes in the aorta and mesenteric arteries were demonstrated by increased incorporation of labelled amino acid (Yamori, 1974, 1976). In SHR 70 days old with significantly higher blood pressure, incorporation of proline into collagenous and non-collagenous protein was significantly increased both in the aorta and mesenteric arteries. In deoxycorticosterone acetate-treated and renal hypertensive rats operated on 1 month previously, proline incorporation into the collagenous proteins of mesenteric arteries was also increased to the same degree at that found in SHR. Thus increased vascular protein synthesis is secondary to hypertension.

Relation between neurological and vascular changes in hypertension

Further analysis of this relation was made in young SHR by incorporation of labelled lysine into mesenteric arteries (Yamori et al., 1976). Labelled lysine incorporation into the non-collagenous protein of mesenteric arteries was already increased in SHR in the pre-hypertensive stage, as reported by Yamabe & Lovenberg (1974).

Furthermore, SHR were treated with the vasodilator hydralazine (Apresoline) or subjected to ganglion blockade (hexamethonium), or they were splanchnicotomized in the pre-hypertensive stage; thus the development of hypertension was effectively arrested for 2 weeks. Lysine incorporation into the non-collagenous protein of mesenteric arteries was already increased in SHR in the pre-hypertensive stage, as reported by Yamabe & Lovenberg (1974).

These results show that neural innervation is important for increased vascular non-collagenous protein synthesis in the pre-hypertensive SHR. They also indicate the close linkage between neurological and vascular changes in the initiation of spontaneous hypertension.

Discussion

The importance of neurogenic factors, which has
been suggested by our various studies, was recently confirmed by concentrations of plasma catecholamine (Grobecker, Roizen, Weise, Saavedra & Kopin, 1975) and dopamine-β-hydroxylase activity (Nagatsu, Kato, Numata & Ikuta, 1974). Nagatsu et al. (1974) showed that plasma dopamine-β-hydroxylase activity is increased only in young SHR. Grobecker et al. (1975) confirmed that plasma levels of both the enzyme and noradrenaline were increased in young SHR. They further suggested the active participation of adrenal medullary catecholamine in adult SHR after the development of hypertension. However, our findings did not support this idea; spontaneous hypertension developed and was maintained in SHR after adrenal medullectomy (Yamori, Yamabe, de Jong, Lovenberg & Sjoerdsma, 1972).

Although neurogenic factors are important in the initial stage of hypertension, they seem to diminish in importance after the establishment of hypertension, as clearly indicated by our noradrenaline turnover study (Yamori, 1974).

Our perfusion (Nosaka et al., 1972) and histological studies (Kyogoku et al., 1972; Yamori & Sasagawa, 1975) indicate that non-neurogenic factors are involved in the maintenance mechanisms of hypertension. The beaded appearance of resistance arteries observed vital microscopically (Ichijima, 1969) is reversible, but subsequently is replaced by structural vascular alterations. Our studies on incorporation of amino acid into the vascular wall (Yamori, 1974, 1976) prove the metabolic basis for such structural vascular alterations. This was also confirmed by Ooshima, Fuller, Cardinale, Spector & Udenfriend (1974), who clearly demonstrated that prolyl-hydroxylase activity is significantly increased in SHR at 50 days and thereafter. They examined various indices of collagen synthesis, and also observed that increased vascular collagen synthesis in SHR and deoxycorticosterone hypertensive rats was suppressed by anti-hypertensive therapy.

These experiments show that the increased collagen synthesis in arterial walls is secondary to hypertension. However, the increased non-collagenous protein synthesis detected in SHR as early as 40 days after birth (Yamabe & Lovenberg, 1974; Yamori, 1976) is influenced by neural innervation (Yamori et al., 1976). Thus the following conclusion can be drawn about the pathogenesis of spontaneous hypertension.

There are initiation and maintenance mechanisms. Neurogenic mechanisms are important for the initiation, whereas the non-neurogenic mechanisms are involved in the maintenance of spontaneous hypertension. Initially the peripheral vascular resistance increases neurogenically, giving rise to labile hypertension. The increased neural tone or pressure load enhances non-collagenous protein metabolism. This then leads to medial hypertrophy, i.e. adaptive structural change in SHR, as well as in essential hypertension. On the other hand, hypertension activates collagenous protein metabolism, i.e., fibre formation which results in hypertensive arteriosclerosis. Adaptive metabolic vascular changes precede adaptive structural change, and they finally increase the non-neural component of peripheral vascular resistance. Our recent findings indicate a close link between initial neurogenic and subsequent vascular mechanisms. These sequential processes seem to be the final common mechanism of hypertension, whatever the primary causes may be. The intervention of some of these initiation and maintenance mechanisms of hypertension was proved to be effective for the therapy and prophylaxis of hypertension.

References


