Beta-adrenoceptor Density and Responsiveness in Borderline Hypertension

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Borderline hypertension (BHT) is characterized by an increase in cardiac index and heart rate at rest and by a normal peripheral resistance. It has been suggested that this reflects an increase in beta-adrenoceptor sensitivity. This study examines the heart rate response to isoprenaline and lymphocyte beta-adrenoceptor density (RD) in BHT.

Isoprenaline sensitivity, defined as the dose of isoprenaline required to increase heart rate by 25 beats/min (CD25), was compared in 20 patients with BHT, 11 normotensives (NT) and 22 patients with essential hypertension (EHT). Isoprenaline sensitivity was not altered in BHT compared with NT. However, the CD25 of patients with EHT was less than in subjects with BHT. RD was significantly greater in subjects with BHT ($P < 0.01$) and EHT ($P < 0.05$) than in normotensive subjects although the difference between subjects with EHT and NT may have been due to age. Furthermore, RD was positively correlated with blood pressure when NT and subjects with BHT were combined.

If the increase in RD which occurs on lymphocytes of patients with BHT also occurs on blood vessels these changes may represent a compensatory mechanism to rising blood pressure which fails as essential hypertension becomes established.

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Introduction

Borderline hypertension (BHT) differs haemodynamically from established essential hypertension (EHT), particularly in young subjects [1], in that cardiac index and heart rate are increased and peripheral resistance is normal [2]. The increase in cardiac output is directly related to an increase in myocardial contractility [3]. These findings are consistent with underlying neurogenic mechanism [4]. One possible mechanism is an increase in beta-adrenoceptor responsiveness. Plasma c'AMP concentrations in response to isoprenaline [5,6] and the chonotropic responsiveness to isoprenaline have been shown to be increased in BHT although largely in subjects with associated symptoms of a hyperkinetic heart [5,7,8]. Other studies have failed to show any change in cardiac sensitivity to isoprenaline in BHT [9-12]. More recently Fraser and colleagues [13] have shown a positive correlation between lymphocyte beta-adrenoceptor density and the chronotropic response to isoprenaline in normal subjects. In this study we examine beta-adrenoceptor function in patients with BHT and relate this to changes in lymphocyte beta-adrenoceptor density.

Methods

The study group consistedof 20 patients with BHT defined as blood pressure which varied above and below 150/90

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dose-response study. The increase in FBF and the decrease in FVR was comparable to that of prazosin (0.5 μg/min/100 ml tissue). Compared to sodium nitroprusside (1.2 μg/min/100 ml tissue) the increase in FBF due to yohimbine amounted to 38% and to prazosin to 30% ($P < 0.05$ for both) and the decrease in FVR due to yohimbine amounted to 76% and to prazosin to 70% ($P < 0.01$). Again, FBF on the right side, intra-arterial mean BP recorded 3 to 5 min after stopping the infusion and HR remained unchanged throughout the study.

Discussion

Blockade of post-junctional alpha-2 adrenoceptors by intra-arterial infusion of yohimbine in normotensive healthy subjects induces a vasodilator response in the forearm which is comparable to that of alpha-1 adrenoceptor blockade and amounts to 38% of the vasodilatory response to sodium nitroprusside. It provides further confirmation of the presence of functionally important postsynaptic alpha-2 adrenoceptors in the human vasculature [4,5]. The increase in FBF of 189% following the infusion of 30 μg/min/100 ml forearm tissue in our study is comparable to that published by van Brummelen *et al.* [4] using a similar intra-arterial dose (194% increase in FBF with 4.0 μg/kg body weight/min).

Before the discovery of postsynaptic alpha-2 adrenoceptors, presynaptic alpha-2 adrenoceptors had been described [8]. They represent an auto-inhibitory feedback system for neuronal noradrenaline release at the junctional level, whereby stimulation of prejunctional alpha-2 adrenoceptors results in a decrease of noradrenaline release. Infusion of the alpha-2 adrenoceptor-blocking agent, yohimbine, should block these prejunctional alpha-2 adrenoceptors with resultant vasoconstriction. However, judging by the comparable vasodilator potency of yohimbine and prazosin, the dilatory effect of yohimbine does not appear to be compromised by a vasoconstrictor component. Lack of evidence of prejunctional alpha-2 adrenoceptor activation has been presented by Kiowski *et al.* [9] who infused the alpha-2 adrenoceptor-agonist, clonidine, into the forearm circulation. Clonidine induced vasoconstriction thus supporting the existence of post-junctional alpha-2 adrenoceptor stimulation, an effect which has been used in treating severe idiopathic orthostatic hypotension [10].

Our evidence for postsynaptic but not presynaptic alpha-2 adrenoceptors may be explained by different locations within the blood vessel wall. Presynaptic alpha-2 adrenoceptors are intrasynaptic and distant from the vessel lumen while postsynaptic alpha-2 adrenoceptors are located extrasynaptically, presumably adjacent to the lumen of the vessel. They could be preferential targets for blood-borne agonists and also for infused compounds, but not sites of action of released transmitter [11,12].

In conclusion, we have demonstrated that post-junctional alpha-2 adrenoceptors make an important contribution to vascular tone in normal subjects. Their role in the increased sympathetic activity of essential hypertension [13-15] where enhanced alpha-1 adrenoceptor-mediated vasoconstrictor tone has already been demonstrated [7] remains to be established.

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