THE EFFECT OF ACUTE AND CHRONIC TREATMENT OF VERAPAMIL ON PRESSOR RESPONSE TO ANGIOTENSIN II IN RATS

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Summary : The effect of verapamil on pressor response to Angiotensin II (A II) was investigated in rats. The responses to A II (10, 20, 40 *ng*, iv) was reduced after verappamil (50 and 100 μg, iv per rat) in a dose dependent manner. Treatment for 5 day with verapamil (18 *mg*/100 *g*/day, po) let to some reduction in basal blood pressure but pressor response to A II was not changed. Treatment for 20 days signicantly reduced the basal blood pressure and increased the responsiveness to A II. it is concluded that Ca^{++} plays a major role in the pressor responses to A II and that chronic treatment with verapamil may reduce basal blood pressure.

Key words : blood pressure verapamil angiotensin II

INTRODUCTION

Over the past decade data has accumulated supporting a major role for renin-angiotensin system in regulating arterial blood pressure and controlling aldosterone secretion in normal homeostasis and disease (3,9). Its role in malignant hypertension, renovascular and high renin essential hypertension is now well documented (5,8). Recent developments have also focussed attention on the value of Ca^{++} channel blockers in malignant hypertension (4). Recently a link between Ca^{++} and renin-angiotensin system has been proposed, The action of angiotensin II (A II) on contraction of some smooth muscles (1,7) and aldosterone release (6,12) have been found to exhibit marked Ca^{++} dependence. These observations, coupled with the ability of nifedipine to reduce the pressor response to A II and adrenaline (11,13) suggest that these drugs may impair the effect of endogenous vasoconstrictors on blood vessels apart from their direct vasodilator action. Present study was hence planned to investigate the effect of acute and chronic administration of verapamil on pressor responses to A II in rats.

MATERIAL AND METHODS

Male albino rats (Wistar strain) weighing 150 to 200 *g* were used. They were allowed normal diet with free access to tap water, In acute experiments carotid artery was cannulated for blood pressure recording and external jugular vein was cannulated for administration of drugs under urethane anaesthesia. The preparation was stabilized for half an hour. When response to A II test dose was reproducible, responses to 10,20, 40 *ng* A II were taken before and 10 minutes after administration of 50 and 100 μg of verapamil. In some experiments, the animals received verapamil (18 *mg*/100 *g*/day, po for 5 days or 20 days) and their sensitivity to A II was determined as above.

RESULTS

The control blood pressure under urethane anaesthesia was 68.6 $\pm$ 8.6 *mm Hg*. A II (10,20,40 *ng*/rat/iv) produced a dose dependent rise in blood pressure (Table I). Administration of verapamil (iv) immediately produced 20-30 mm Hg fall in blood pressure, which recovered partially and settled below the initial basal line within 10 minutes (Fig. 1). The pressor responses to A II were reduced after 50 and 100 μg of verapamil (iv) in a dose dependent manner.

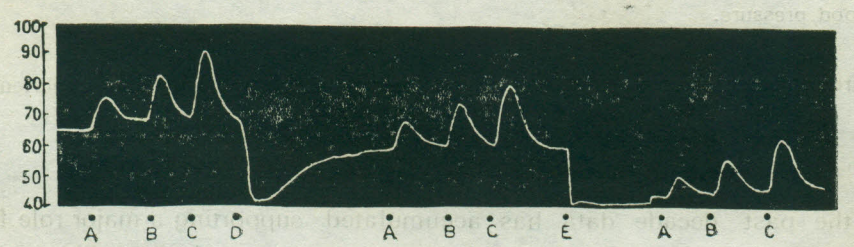

Fig. 1 : Effect of Verapamil on pressor responses to angiotensin II in rat.

A 10 ng AII
B 20 ng AII
C 40 ng AII
D 50 μgV
E 100 μgV

(1 m.m. = 1 mm Hg)

Effect of short term treatment with verapamil (18 *mg*/100 *g*/day, po for 5 days) on the pressor responses to A II was not significantly different from control animals. However, long term treatment for 20 days significantly reduced the mean basal blood pressure and increased the responsiveness to A II (Table I).

TABLE I : Effect of acute and chronic treatment with verapamil on rise in blood pressure (△ mm Hg due to iv angiotensin II (A II) in rats.

A II (ng)	Before verapamil	After verapamil			
		Acute iv bolus		18 mg/100 g/day oral	
		50 μg	100 μg	5 days	20 days
10	10.33±1.16	3.85±0.75*	1.90±0.53*	10.75±2.25	17.23±2.13*
20	15.66±1.62	9.33±1.37*	6.23±1.29*	18.0±3.53	22.8±2.0*
40	22.0±2.3	12.66±2.0*	10.0±1.33*	20.52±4.29	32.0±2.3*

Mean basal blood pressure : control group, 68.6 ± 8.6 mm Hg; 5 days treated group, 66. 25± 2.4 mm Hg and 20 days treated group, 61.4 ± 8.6 mm Hg.

*Value differs significantly ($P < 0.01$) from 'before verapamil' values.

DISCUSSION

Angiotensin is capable of stimulating Ca^{++} influx and also releasing intracellular Ca^{++} thereby initiating smooth muscle contraction (1, 12). Interference of verapamil with pressor responses to A II reaffirms the above finding. The complete recovery of vascular responsiveness to A II after 90 min, of iv administration of verapamil observed in control experiments excludes the possibility of techyphylaxis to A II. The reduced pressor responsiveness to A II following verapamil may either be due to inhibition of the pressor action of A II which is a Ca^{++} dependent process (2) or a consequance of verapamil induced vasodilatation. The first effect seems to be predominating since decreased vascular tone caused by verapamil prior to A II should have led to increased pressor effect of A II (11).

Vierhapper and Waldhausl (13) and Millar *et al.* (11) recently demonstrated attenuation of hypertensive response to A II and noradrenaline following oral treatment of nifedipine for 7 days in normal healthy subjects. It will be of interest to know the effect of chronic verapamil treatment on noradrenaline response in rats.

However, in the present study the oral treatment of verapamil for 5 days led to insignificant reduction of basal blood pressure and pressor response to A II. In contrast significant increase in pressor response to A II with low basal blood pressure was observed following chronic treatment with verapamil for 20 days, This increased responsiveness to exogenous A II could be due to low basal blood pressure or/and decreased

endogenous A II leading to upregulation of receptors. The later suggestion has further been supported by markedly reduced levels of PRA in these chronically treated animals (authors unpublished data), but relevance of this suggestion needs to be further examined.

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