ANGIOTENSIN INDUCED CHANGES IN BLOOD GLUCOSE LEVEL

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Summary: Angiotensin given by intravenous route in rabbits caused a marked rise in blood glucose within 45 min. Guanethidine, bretylium, alpha methyl DOPA, adrenalectomy and reserpinization significantly influenced the changes in blood glucose induced by angiotensin II. It is suggested that the rise in blood glucose level induced by angiotensin II appears to be mediated by facilitation of catecholamine release or due to inhibition of reuptake.

Key words: angiotensin catecholamines hyperglycaemia

INTRODUCTION

Angiotensin is one of the potent pressor agents known at present. A number of pressor agents have metabolic effects. Forte *et al.* (9) and Heidenreich *et al.* (12) have reported a slight but significant rise in blood glucose level in dogs and man. The reports of Mortiz *et al.* (16). Healy *et al.* (11), Rengo *et al.* (19), Nakano and Kusakari (17) and Johnson *et al.* (14) on the effect of angiotensin on blood glucose level are conflicting. Moreover, angiotensin markedly interferes with the autonomic nervous system activity and has been shown to be endogenous to brain (1). A number of workers have reported the involvement of central nervous system in the control of blood glucose level (4,5,7,10,20).

On account of the importance of angiotensin in severe or malignant hypertension (15) and its relation with release of catecholamines (6, 8) it was thought of interest to investigate the effect of intravenous administration of angiotensin II on blood glucose level in rabbits.

MATERIALS AND METHODS

Adult albino rabbits of either sex weighing between 1-2 *kg* were used in present study. They were anaesthetized with 10% chloralose solution (80-100 *mg/kg* i.v.) in normal saline. The anaesthesia was maintained by subsequent intravenous chloralose, if necessary. In all the rabbits a constant ventilation of the lungs was maintained by intubating the trachea and connecting it to a pulmoflator. The femoral vein was exposed and a polythene catheter was indwelt for taking successive samples of blood and to infuse saline and drugs whenever required. The standard dose of angiotensin II (Hypertensin, Ciba) used was 10 $\mu g/kg$ in 2 *ml* normal saline for intravenous injection. The blood samples were obtained in fluoride tubes just before injection and subsequently at 15 min intervals upto 120 min. Blood glucose was determined according to the technique of Asatoor and King as described by Varley (22).

Guanethidine (10 $\mu g/kg$/day i.v.) or bretylium (28 $\mu g/kg$/day by stomach tube or alpha-

methyl DOPA (25 $\mu g/kg$/day orally by stomach tube) were given orally for 4 days prior to the experiment and angiotensin was administered on the 5th day. Adrenaline (1 $\mu g/kg$/min) was infused for 15 min and after 30 min angiotensin was given intravenously. Reserpine was administered intraperitoneally, 1 mg/kg on the first day followed by 0.5 mg/kg on two consecutive days (21). Angiotensin was administered 24 hr after reserpine treatment.

Effects of angiotensin were also extended to adrenalectomized and reserpinized-adrenalectomized rabbits.

RESULTS

Angiotensin administered intravenously in a dose of 10 $\mu g/kg$ caused a significant rise in blood glucose level from 90 $\pm$ 3 $mg\%$ to 136 $\pm$ 5 $mg\%$. The maximum rise was obtained at 45 min and reached the normal level within 2 hr (Table I).

Table I: Effect of intravenous administration of angiotensin II on blood glucose in rabbits under different experimental procedures.

Mean blood glucose level $\pm$S.E. ($mg\%$)

Time (min)	*Normal rabbits*	*Guanethidine pretreatment*	*Bretylium pretreatment*	*Alpha methyl DOPA pretreatment*	*Adrenalectomized*	*Reserpinized*	*Resperpinized adrenalectomized*	*After adrenaline*
Control	90±3	86±4	83±3	78±5	75±4	93±4	79±4	124±5
15	116±4	88±4	86±5	81±4	77±4	95±3	80±5	139±4
30	128±4	91±3	89±3	88±5	82±5	99±5	82±3	204±5
45	136±5	96±4	90±4	94±3*	91±4*	102±5	84±5	227±4
60	130±5	93±5	89±4	93±4	87±3	96±3	84±5	221±5
75	126±3	91±4	87±3	92±3	84±4	96±4	82±3	217±4
90	108±4	90±3	86±4	88±4	82±5	94±4	81±4	186±3
105	97±5	89±5	85±5	85±3	78±4	92±3	81±4	141±5
120	92±4	84±4	81±5	81±4	73±4	92±3	81±4	137±5
	n=10	n=8	n=8	n=8	n=8	n=8	n=8	n=88

* Probability of significance (<0.05) from the corresponding control levels.

Pretreatment with bretylium, guanethidine, or reserpine completely blocked the effect of angiotensin on blood glucose (Table I). Pretreatment with alpha-methyldopa or adrenalectomy also blocked the hyperglycaemic effect of angiotensin, but at 45 min the blood glucose levels were still higher ($P<0.05$) than the corresponding control blood glucose levels (Table I). In reserpinized and adrenalectomized animals there was a complete block of the hyperglycaemic effect of angiotensin.

Intravenous angiotensin given after exogenous intravenous adrenaline caused a steep,

substained and more marked rise in blood glucose level from 124 ± 5 *mg*% to 227 ± 4 *mg*% after 45 min (Table I).

DISCUSSION

The present investigation has shown that during angiotensin administration the rise in fasting blood glucose level is rapid and of short duration. This finding is in direct agreement with the results of Akinkugbe (2) and Bogdanowicz (3). Nakano and Kusakari (17) however, have reported a decrease in blood glucose level by angiotensin in dogs.

Adrenaline is known to cause hyperglycaemia due to its glycogenolytic action and angiotensin belongs to a unique class of naturally occurring substances, capable of modifying the adrenergic functions via a neurogenic mechanism (13). It has been suggested that angiotensin can increase the amount of catecholamines released during nerve stimulation (6). Adrenaline liberated in this manner also has an inhibitory effect on insulin response to hyperglycaemia (10). However, others have presented evidence that the polypeptide acts by preventing the re-uptake of catecholamines into sympathetic nerves (18). It can be suggested on the basis of our findings that facilitation of catecholamine release is the major effect on the interaction between angiotensin and sympathetic nerve terminals and that this effect depends upon the presence of sympathetic nerve activity. It is supported by our findings of a no increase in blood glucose level by angiotensin in guanethidine, bretylium and reserpine pretreated rabbits, and less increase in alpha-methyldopa pretreated rabbits.

It has also been postulated that angiotensin liberates catecholamines from adrenal medulla (8). This fact may be contributing in angiotensin induced hyperglycaemia as the rise was less in adrenalectomized animals as compared to normal rabbits and exogenous adrenaline potentiated the hyperglycaemic effect of angiotensin. Besides a complete block of the hyperglycaemic effect of angiotensin in adrenalectomized-reserpinized rabbits also indicates the involvement of catecholamines in angiotensin-induced hyperglycaemia in rabbits.

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