

## MODIFICATION OF HYPERGLYCAEMIC EFFECT OF ANGIOTENSIN BY INDOMETHACIN

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**Summary:** Effect of angiotensin II was studied on blood sugar level in dogs. Angiotensin given by intravenous route caused a marked rise in blood sugar level. Indomethacin and propranolol significantly influence the changes in blood sugar level induced by angiotensin. It is suggested that the hyperglycaemia induced by angiotensin appears to be mediated by facilitation of adrenaline and prostaglandin release.

**Key words :** angiotensin II      hyperglycaemia      indomethacin      propranolol

### INTRODUCTION

Angiotensin is one of the most potent pressor agents known at present. A number of pressor agents have metabolic effects. Contradictory reports are available regarding the effect of angiotensin on blood sugar level. Forte *et al.* (9) and Heidenreich *et al.* (11) have reported a slight but significant rise in blood glucose level in dogs and man. Iizuka *et al.* (13) did not find any significant change in blood glucose level. While Nakano and Kusakari (16) reported a fall in blood glucose level following infusion in dogs. 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 (10,19).

Taking into the consideration the importance of angiotensin in severe or malignant hypertension (14) and its relation with release of catecholamines (7,8) and prostaglandins (2,20) it was thought of interest to investigate the effect of intravenous administration of angiotensin II on blood sugar level in dogs and to study the involvement of prostaglandins in the hyperglycaemic effect of angiotensin.

### MATERIALS AND METHODS

Forty-eight mongrel dogs of either sex weighing between 8-14 were used in present study. They were anaesthetized with 10% chloralose solution (80-100 mg/kg) in normal saline. The anaesthesia was maintained by subsequent intravenous chloralose. In all the dogs a constant ventilation of the lungs was maintained by intubating the trachea and connecting it to an artificial respirator. 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 (Hypertension, Ciba) used was 1  $\mu\text{g}/\text{kg}$  in 2 ml normal saline. The animals were kept on water for 10 hours before experimentation. The blood



samples were taken in fluoride tubes just before injection (initial) and subsequently at 10 min intervals upto 120 min. Fasting blood sugar was determined according to the technique of Asatoor and King as described by Varley (21). Indomethacin (2 mg/kg) was administered by intravenous route 24 hours prior to the experimentation (2). Propranolol (4 mg/kg intramuscularly) was used as adrenergic  $\beta$ -receptor blocking agent (4).

## RESULTS

### Effect of intravenous administration of angiotensin in normal dogs :

Intravenous administration of angiotensin caused a marked rise in mean blood sugar level from initial value of  $58.9 \text{ mg} \pm 7.4 \text{ mg} \%$  to  $129.5 \pm 7.9 \text{ mg} \%$ . The maximum rise was obtained within 30 min and reached to the initial (normal) level within 120 min (Table I, Fig. 1).

TABLE I: Effects of intravenous administration of angiotensin on blood sugar level in dogs following different experimental procedures.

No. of experiments	Experimental procedures	Initial blood sugar	Maximum rise in blood sugar level
		(mg%) Mean $\pm$ SD	(mg%) Mean $\pm$ SD
12	Normal	$68.9 \pm 7.4$	$129.5 \pm 7.9^*$ (P < 0.001)
12	Indomethacin pretreatment	$66.2 \pm 6.4$	$109.6 \pm 7.2^{**}$ (P < 0.001)
12	Propranolol pretreatment	$65.7 \pm 6.5$	$86.8 \pm 5.8^*$ (P < 0.001)
12	Indomethacin and propranolol pretreatment	$69.4 \pm 6.6$	$71.8 \pm 7.2^*$ (P > 0.05)

\*Statistical analysis by students' t test.

### Effect of intravenous administration of indomethacin pretreated dogs :

When angiotensin was given in indomethacin pretreated dogs, there was less rise in mean blood sugar level from a initial value of  $66.2 \pm 6.4 \text{ mg} \%$  to  $109.6 \pm 7.2 \text{ mg} \%$  after 30 min (Table I, Fig. 1).

### Effect of intravenous administration of angiotensin following propranolol pretreatment :

Intravenously administered angiotensin produced a small rise in mean blood sugar level in propranolol pretreated dogs from a initial value of  $65.7 \pm 6.5 \text{ mg} \%$  to  $86.8 \pm 5.8 \text{ mg} \%$  (Table I,



Fig.1). The maximum rise was determined within 40 min which returned to the initial (normal) level within 120 min.

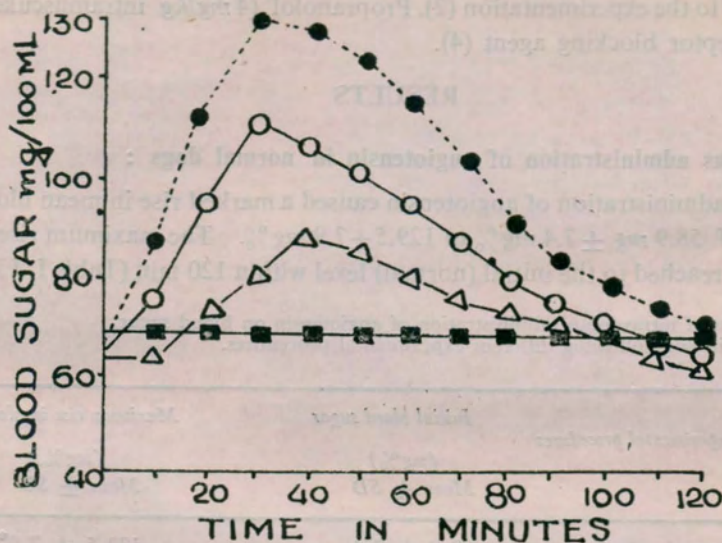


Fig. 1: Effects of intravenous administration of angiotensin on blood sugar level in dogs following different experimental procedures.

- Normal dogs.
- indomethacin pretreated dogs.
- △—△ Propranolol pretreated dogs.
- Indomethacin and propranolol pretreated dogs.

#### Effect of intravenous administration of angiotensin following indomethacin and propranolol pretreatment :

The rise in blood sugar level was not obtained in indomethacin and propranolol pretreated dogs, having initial mean blood sugar level of  $69.4 \pm 6.6$  mg% which rose to  $71.8 \pm 7.2$  mg% Talbe I, Fig. 1).

#### DISCUSSION

Present investigators reveal that during angiotensin administration the rise in fasting blood sugar level is rapid. This finding is in direct agreement with the results of Akinkugbe (3) and Bodganowicz *et al.* (6). The magnitude of hyperglycaemia is less marked in indomethacin pretreated dogs in which prostaglandin synthetase was inhibited (22). This indicates that prostaglandin release is one of the factors which cause a rise in blood sugar level when angiotensin was administered intravenously. Bergstrom *et al.* (5) demonstrated that prostaglandins cause a rise in blood sugar level 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 (12). It has been suggested that angiotensin can increase the amount of catecholamines released during nerve stimulation (7). Adrenaline liberated in this manner also has an inhibitory effect on insulin response to hyperglycaemia (10). Moreover, others have presented evidence that the polypeptide acts by preventing the reuptake of catecholamines into sympathetic nerve (7). It can be suggested on the basis of our findings that facilitation of catecholamine (mostly adrenaline) 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 small rise in blood sugar level by angiotensin in propranolol pretreated dogs. It has also been postulated that angiotensin liberates adrenaline from adrenal medulla (8). This fact may be contributing in angiotensin induced hyperglycaemia as the rise was less marked in propranolol pretreated animals as compared to the normal dogs.

It is suggested that intravenous administration of angiotensin causes a marked release of catecholamines mostly adrenaline which is responsible for major part of hyperglycaemia and it also releases prostaglandins which contribute a smaller part of hyperglycaemic effect. Role of prostaglandin albeit small appears to be significant in view of the recent demonstrations by Malik and McGiff (15) that angiotensin is a potent stimulant of prostaglandin synthesis in a number of tissues and the presence of prostaglandins in pancreas in a variety of species (18). These observations further support the involvement of prostaglandin in angiotensin induced hyperglycaemia.

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