HYPOCHOLESTEROLEMIC RESPONSE TO ANGIOTENSIN II IN DOGS

K.N. SINGH, R.K. MITTAL, K.C. MANCHANDA AND J. KUMAR

Department of Physiology,
M.L.N. Medical College, Allahabad

Summary: Intravenous administration of angiotensin II caused a significant decrease in blood cholesterol level in dogs. This hypocholesterolaemic response, also obtained in spinal vagotomized and adrenalectomized dogs, indicates that central nervous system and adrenals have no role in angiotension II induced hypocholesterolemic effect. In hepatectomized dogs in which both vagi were intact intravenously administered angiotensin did not cause any significant decrease in blood cholesterol level, suggesting that angiotensin exerts its effect by inhibiting the synthesis or preventing the release of cholesterol from the liver.

Key words : Angiotensin, blood cholesterol, spinal vagotomy, hepatectomy, adrenalectomy

INTRODUCTION

Cholesterol plays a significant role in arterial atherosclerosis. In the body, cholesterol is distributed in the free form, and the esterified form. It is assumed that it is the esterified form which changes with dietary, hormonal and other variations (1).

Angiotensin causes vasoconstriction by its direct action on vascular smooth muscles and by releasing the catecholamines from central as well as peripheral stores specially adrenal medulla (7,9).

Reports on lipid metabolic changes related to angiotension II are conflicting. Heindenreich *et al.* (3) observed a slight fall in free fatty acid when angiotensin was infused in dogs while Nakano and Kusakari (6) reported decrease in plasma free fatty acid in anaesthetized dogs during infusion of angiotensin. But, Iizuka *et al.* (4) did not find any change in plasma free fatty acid level in normal as well as in atropine pretreated dogs during infusion of angiotensin.

The available literature does not speak of the effect of angiotensin II on blood cholesterol. This has been investigated in dogs.

MATERIALS AND METHODS

Dogs of either sex weighing 8-14 *kg* were used in the present study. They were anaesthetized with pentobarbitone sod. (30 *mg/kg*) dissolved in normal saline at room temperature. The anaesthesia was maintained by subsequent intravenous pentobarbitone sod. if necessary. In all the dogs 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 the successive samples of blood and to infuse saline and drug whenever required. The standard dose of angiotensin II (hypertensin, Ciba) used was 3 *μg/kg* (i.v.) dissolved in 2 *ml* normal saline.

In eight dogs denervation was done by cutting both the vagi and spinal cord transection at C_2 level according to the technique of Singh *et al.* (7). In eight dogs bilateral adrenalectomy was also done. In five dogs hepatectomy was done by a midline incision, extending downwards upto the umbilicus. The abdominal retractor was applied and all the lobes of the liver were exposed and tied at their root by a thread. The portahepatis was exposed and ligated properly. All the ligaments connected to the liver were cut and the liver as a whole was removed. During this surgical procedure, 500 *ml* of normal saline was infused intravenously.

The blood samples were obtained in double oxalate tubes just before injection and subsequently at 15 min interval upto 60 min, then at 30 min interval upto the next 120 min. The total blood cholesterol was determined according to the technique of Sackett as described by Varley(8). The results are expressed as mean ± S.D.

RESULTS

Effect of intravenous administration of angiotensin in normal dogs:

Intravenous administration of angiotensin II caused a significant decrease ($P<0.01$) in mean blood cholesterol level to 108.6 ± 9.8 *mg* from a control mean value of 146.2 ± 10.2 mg. The maximum decrease in blood cholesterol level was observed within 60 min followed by a gradual increase reaching its normal level within 180 min (Fig. 1).

Effect of intravenous administration of angiotensin following spinal section and bilateral vagotomy, adrenalectomy and hepatectomy:

Following spinal section and bilateral vagotomy in eight anaesthetized dogs angiotensin II again caused a significant decrease ($P<0.01$) in mean blood cholesterol level to 100.8 ± 11.4 *mg* from a control mean value of 147.9 ± 9.7 *mg*. The maximum decrease in blood cholesterol was observed within 60 min which gradually returned to its control level within 180 min. (Fig. 1).

Following adrenalectomy angiotensin produced a significant decrease ($P<.01$) in mean blood cholesterol level to 110±10.5 *mg%* from a control mean value of 152.1±9.2 *mg%*. The maximum decrease in blood cholesterol was observed within 60 min which gradually returned to the basal level within 180 min (Fig. 1).

Following hepatectomy angiotensin II did not cause any significant decrease ($P>0.1$) in mean blood cholesterol level (level 134.7 ± 11.7) *mg%* from a control mean value of 136.6 ± 8.4 *mg%*.

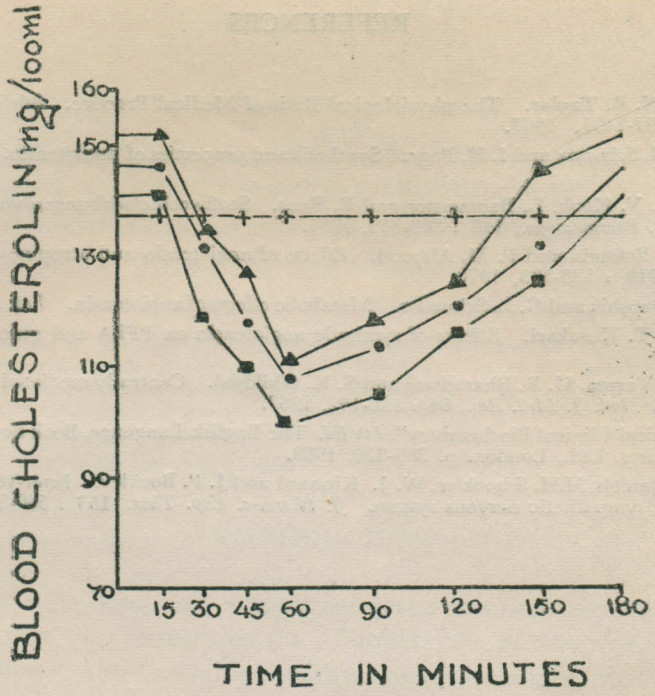

Fig. 1: Effect of intravenous administration of angiotensin II on blood cholesterol level in normal dogs(●——●), dogs subjected to spinal transection and bilateral vagotomy(■——■) dogs subjected to bilateral adrenalectomy (▲——▲) and dogs subjected to hepatectomy (+——+) The points shown are the mean points. Standard deviations are not shown to maintain clarity.

DISCUSSION

Kaley *et al.* (5) reported that intravenous injection (5 $\mu g/kg$) or infusion (1 $\mu g/kg$)/*min* of angiotensin significantly lowered the free fatty acids concentration of plasma in the unanaesthetized dogs. *In vitro* experiments on perfused rat liver suggested that angiotensin stimulates the free fatty acid uptake by the liver via mechanism(s) independent of its own vasoconstrictor action.

In the present study intravenous administration of angiotensin II caused a significant decrease in blood cholesterol level. This hypocholesterolemic effect was also observed in spinal vagotomized and adrenalectomized dogs which indicates that central nervous system and adrenals have no role in lowering blood cholesterol level by angiotensin II. The decrease in blood cholesterol level was not obtained in hepatectomized dogs. It is suggested that intravenous administration of angiotensin produced a significant decrease in blood cholesterol level by acting directly on the liver. It could not be ascertained whether this effect was due to inhibition of cholesterol synthesis or prevention of its release from the liver.

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