DISCUSSION
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Intensive researches were carried out during the last few decades to find out the causes and control of hypertension.

It was reported that areas of central nervous system involved in the regulation of blood pressure are mainly associated with hypothalāmūs and brainstem area extended to thoracic spinal cord. (Press, 1965).

Several investigators also suggested the role played by different neurotransmitters in controlling the calibre of blood vessels thereby regulating blood pressure (Naranjo and Naranjo, 1958; Collis et al, 1979).

Moreover, the reflex responses arising from baroreceptors depend on the changes of the calibre of arteries and are affected by tissue metabolites like histamine, serotonin etc. associated with hypertension (Aars, 1975).
Hypertension can also be produced in experimental animals by renal arterial occlusion (Goldblatt's method). Increasing evidences suggest that the renin-angiotensin system plays a substantive role in the pathogenesis of renal arterial hypertension. In hypoxia, renin is released by the juxtaglomerular cells of kidney. This released renin then acts on a basic substance angiotensinogen (a circulating $\alpha_2$ globulin manufactured in the liver) to form the decapeptide angiotensin I. Angiotensin I is then enzymatically converted by converting enzyme to the octapeptide angiotensin II in the liver by splitting off the two C-terminal amino acids. This angiotensin II is a potent pressor compound and it exerts this pressor action by a direct effect on arteriolar smooth muscle (Harrison, 1982).

Other evidences exist to suggest the role of mast cells in different perivascular tissues by releasing vasoactive and chemotactic principles like histamine, serotonin, heparin etc. (Oomen, A.P. 1979; Purcell et al., 1989).
There are several controversies regarding the role of histamine in hypertension. Riley and West (1953) elucidated the association of histamine with mast cell which is known to liberate histamine. They also reported, that with less number of mast cells, there is considerable decrease in histamine content in tissues and vice-versa. Dale and Laidlaw (1910) first suggested the vasodepressor effect of histamine though other investigators (Feldberg, 1927) claimed the existence of a biphasic role of histamine on blood pressure: constrictor action on large arteries while dilator effect on capillaries.

It has been further suggested by Hackenthal et al (1983) that histamine stimulates the adenylate cyclase activity and thereby increases the renin release from isolated perfused rat kidney resulting in an experimental hypertension.

Besides, Pelvin & Boarder (1988) found the stimulatory effect of histamine on the catecholamine release from bovine adrenal medullary chromaffin cells and Noble et al (1988) interpreted that histamine plays an essential role in controlling the physiology and biochemistry of adrenal medullary chromaffin cells.
Recently, Choi et al (1993) reported that histamine evokes greater increase in catecholamine secretion in epinephrine containing chromaffin cells in comparison to the norepinephrine containing cells.

In our present study, it has been observed that mast cell count in different perivascular tissues like kidney cortical and medullary tissues, lung and mesentery showed no significant alteration after 7 days of production of experimental hypertension followed by an increase after 14 days which was maintained upto the 21st day of study (except spleen tissue).

Our observation further shows that histamine concentration in serum as well as in lung, spleen and mesentery was elevated throughout the experimental period in comparison to the control group. Maximum elevation was attained on 14th day of experiment except in kidney cortical and medullary tissue which showed no significant alteration on the 7th day of experiment but was followed by significant rise on 14th and 21st day following production of hypertension in respect to the corresponding control group.
As our investigation focussed that mast cell population in different tissues has increased from the 14th day of the experiment except the spleen tissue in comparison to the sham operated control group, it might be elucidated that the rise in histamine content in those tissues (except in kidney where rise occurred on the 14th day) was possibly due to their release from the mast cells of the respective tissues.

Considering the blood pressure level of the experimentally induced hypertensive rabbits, an elevation of blood pressure was observed in comparison to the sham control group (Table-I). Since, it was earlier reported that histamine exhibits a biphasic role i.e. both vasodilator and vasoconstrictor actions (Feldberg, 1927) it would be reasonable to suggest that there should have been no alteration in blood pressure of the experimental groups of animals in comparison to their control groups.

However, as there are several other reports to indicate that histamine stimulates the catecholamine release (Choi et al 1993) activates the release of renin (Hackenthal, 1983) and potentiates the action of angiotensin II (Zengil, 1981) it
might be speculated that the rise in blood pressure is an effect of the above modes of actions of histamine.

Besides, our present investigation shows a rise in DAO, the degrading enzyme for histamine on the 7th and 21st day of the experiment. This probably is responsible for the diminution of histamine, considered to take part as a potent vasodilator (Lüscher, 1994). This indirectly causes a rise in blood pressure level in the experimental group of animals in comparison to the control (sham operated) Serum level of DAO also showed the same picture.

Controversies also exist regarding the role of serotonin (5-HT) in hypertension. Erspamer (1940) first isolated and identified serotonin as a vasoconstricting agent and Parratt and West (1957) reported its occurrence in different tissues of mammals and found a close association of this amine with mast cell.

Collis et al (1979) surmised that 5-HT may potentiate the release of norepinephrine and angiotensin II which was further supported by Myers et al (1985).
Davies et al. (1991) demonstrated that serotonin directly stimulates calcium uptake in zona glomerulosa cells of adrenal cortex via calcium channels which are coupled to specific serotonin receptors.

Besides, Fuder et al. (1994) found that serotonin receptors 5HT-3 or 5HT-4 subtypes are known to facilitate acetylcholine release upon compound 48/80 exposure. Such pre-junctional modulation of autonomic neurotransmitter release is accompanied by release of mediators from the mast cells.

Recently, Lefebvre et al. (1995) suggested that in rats, 5HT potentiates the stimulatory effect of angiotensin II on aldosterone secretion but in human it has no such effect.

In our present study, it has been observed that in serum and lung tissue a elevation of serotonin content is found throughout the experimental period as compared to the control group though the maximum rise occurred on 7th day of experiment.
In kidney medullary and mesentery, elevation of serotonin level was found on day 7 and 14 as compared to the corresponding control group followed by a marked decrease in serotonin level on 21st day after production of hypertension with respect to the control group.

In kidney cortical tissue and spleen tissue no significant alteration is found on 7th and 14th day of experiment following production of hypertension as compared with the corresponding control group. However, on 21st day following production of hypertension, the serotonin concentration rises significantly in kidney cortical tissue whereas it decreases significantly in spleen tissue of experimental group as compared to the sham operated control group.

Just like histamine, serotonin also exhibits a biphasic role i.e. it has both dilator and constrictor effect and as such, it might be speculated that the variations in blood pressure level observed in the above mentioned preparations are a reflection of this dual role of serotonin (Sole et al., 1988).

It has been reported that serotonin causes
vasodilatation of the arterioles via $S_1$ receptors but in venules and capillaries it causes vaso constriction through $S_2$ receptors (Buccino et al 1967; Sole et al 1970). Thus it can be suggested that the effects of serotonin are diverse as activation of $S_1$ and $S_2$ receptors results in opposite types of effects on blood pressure (Gillis et al 1988).

Considering this biphasic role of serotonin there should have been no change in blood pressure, although in our present investigation a rise in blood pressure level observed. A reasonable explanation may be put forward for this rise in blood pressure level.

Recently, Pergola and Alper (1991) reported that serotonin injected into the lateral cerebral ventricle of conscious rats induces sympathoexcitation and release of vasopressin and thus resulting in an increase in mean arterial pressure.

Besides, it has been demonstrated that serotonin potentiates the release of NE & angiotensin II (Collis et al, 1979; Myers et al, 1985), causing thereby a rise in blood pressure level.
Probably the vasoconstrictor effect of serotonin (by potentiating the effects of other vasoconstrictors like NE, angiotensin II, vasopressin etc.) is more pronounced than its vasodilator action and this might be the cause of the increased blood pressure level observed in the present study.

Heparin was first discovered by Mclean in 1916 in Howell's laboratory. Holmgren and Wilander (1938) found the close association of heparin with mast cells. Its antithrombic and vasodilator action were reported by Fitz Gerald et al (1967) and Hales et al (1983) respectively.

Susic et al (1982) reported that heparin causes a significant increase in cardiac output and a significant decrease in total peripheral resistance and packed cell volume. However, the blood pressure lowering effect of heparin may be attributed to a decrease in packed cell volume.

Vasdev et al (1994) revealed increased calcium uptake in vascular tissue leading to elevated cytosolic free calcium which was implicated with the pathogenesis
of hypertension. High dose of low molecular weight heparin normalizes the elevated platelet cytosolic free calcium, aortic calcium uptake and systolic blood pressure in spontaneously hypertensive rats, but it had a limited effect on adverse renal vascular changes.

Gang et al (1976) observed that intravenous injection of heparin is promptly followed by marked rise of plasma diamine oxidase (DAO) level. Wolvekamp and deBruin (1994) found that after intravenous administration of heparin DAO is released from its capillary binding sites in the lamina propria into the peripheral circulation.

In our present study, heparin in serum and different tissues rises significantly throughout the experimental period in respect to the control group except mesentery which showed significant decrease on 14th day after production of hypertension and kidney medullary tissue showed marked rise on 7th day of the experiment in comparison to the control group.
As heparin is a vasodilator it seems that it must produce a fall in blood pressure level. However, in our present investigation an elevation of blood pressure was recorded and it might be suggested that since heparin stimulates the release of DAO that catabolises histamine (vasodilator) there is an indirect reflection in the blood pressure level i.e. an elevation.

There is adequate evidence to suggest the possibility that noradrenaline (NA) also elicits hypertensive effect and increases the blood pressure level.

It has been proposed that electrical stimulation of hypothalamus of rats and cats causes rise in blood pressure by enhancing the release of catecholamine (Philippu et al, 1971). It was found that in experimentally produced neurogenic hypertension increased blood pressure is associated with increased turnover of NE (Chalmers, 1975).

Noradrenaline (NE) also exhibits constricting effect on mesenteric, renal, splanchnic and hepatic levels and thereby produces increased resistance
and elevation of blood pressure (Hoffman and Lefkowitz, 1991).

In our present study, noradrenaline content of serum as well as different tissues like kidney, lung, spleen and mesentery were found to be elevated throughout the experimental period in the experimental group in respect to the control group.

It may be surmised that noradrenaline by its constrictor action induces an increase in peripheral resistance thus resulting in high blood pressure. Moreover, since in our present finding we have already noticed a rise in histamine and serotonin content which are known to possess stimulatory action over the release catecholamine (Myers et al, 1985; Choi et al, 1993), it might be thought that noradrenaline through the release of serotonin and histamine may bring about a rise in blood pressure level.

Born (1994) recently demonstrated that uptake or LDL is significantly increased by noradrenaline and adrenaline at their pathophysiological blood concentration. This suggests that in these animals this pathophysiologic changes could help
to account for hypertension though the exact mechanism is still under investigation.

Serum cholesterol level is considered to be a vital factor for inducing hypertension indirectly by increasing the development of atherosclerosis. If there is hyperlipidaemia it accelerates the process of atherosclerosis which contributes much in the elevation of blood pressure (Park & Park, 1991).

Considerable evidences also exist that suggest certain alterations in the lipid profile in hypertension such as increase of low-density-lipoprotein, cholesterol and triglycerides (Weidmann et al, 1988). It has been observed that in anaesthetised rabbits and in conscious rats the uptake of LDL is significantly increased by noradrenaline and also by adrenaline (Born 1994).

Since the mast cells enhance the release of noradrenaline which again plays a passive role in increasing the cholesterol and lipoprotein levels, the rise in serum triglyceride and cholesterol level observed in our present
study may be attributed to a rise in noradrenaline level released from the mast cells.

Thus, the elevated serum triglyceride and cholesterol level in the experimental group in comparison to the control group play a passive role in inducing hypertension by accelerating atherosclerotic processes.

Therefore, the present findings give a strong indication that a number of components released from the mast cells are directly or indirectly involved in the elevation of blood pressure observed in experimentally induced hypertensive animals (renal hypertension).