REVIEW OF LITERATURE
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The name 'Mast Cell' was taken from the German word 'masten' meaning 'to feed' when their cytoplasmic granules were believed to be products of phagocytosis. Two types of mast cells, mucosal and connective tissue were reported in rodent tissues back in the 1960's on the basis of histochemical and fixation techniques. Mast cells are present in most of the perivascular tissues like lung, stomach, spleen, mesentery, kidney etc and they are known to possess a variety of vasoactive and chemotactic mediators (Riley and West, 1953; Parratt and West, 1957). Several reports suggest that mast cells from different species and from different sites in the same species differ markedly in their responsiveness to mediator release (Rothschild, 1966; Assem and Monger 1970; Schmutzler et al, 1978; Pearce and Ennis, 1980). Wasserman showed in 1979 that in antigen induced hypersensitivity reactions, the mast cells function as the effector cell armed with an arsenal of preformed mediators and with the ability to synthesize additional biological agents, which when released in response to the appropriate stimulus, effect dramatic changes in surrounding target tissues like blood vessel, smooth muscle etc.

Middleton et al (1981) described that mast cell mediators are derived from three sources:

1. Preformed Primary mediators which are loosely bound
to the granular matrix - histamine ECF - A, intermediate weight ECF - A and NCF - A (Neutrophil chemotactic factor of anaphylaxis).

2. Newly formed mediators generated in response to the immunologic reaction - prostaglandings, (Slow reacting Substance - anaphylaxis) SRS – A, Kallikrein and bradykinin.

3. Granule - associated mediators released slowly with granular dissolution - heparin, superoxide dismutase, peroxidase aryl-sulfatase A.

Schwartz (1994) demonstrated that preformed mediators which are stored in the secretory granules are secreted upon cell activation. These include biogenic amines like histamine, serotonin etc. proteoglycons either heparin, oversulfated condroitin sulphates and a spectrum of neutral proteases. The proteoglycon imparts the metachromatic staining characteristics of mast cells when exposed to basic dyes like toluidine blue. Newly generated mediators, often absent in resting mast cell consist of arachidonic acid metabolites, principally leukotriene C₄ and prostaglandin (PG) D₂ and cytokines.
No specific physiological mechanism has been identified which promotes or regulates the release of any or all of these mediators. One of the trigger for degranulation appears to be a type I antigen - antibody reaction on the surface of the mast cells which have been sensitised by cell bound IgE antibody as a result of previous exposure to antigen (Murphy, 1981).

Ishijaka et al (1980) found that when mast cells are exposed to antigen, they become activated by cross linking surface bound specific IgE which in turn causes secondary bridging of the IgE - Fc receptors and lead to membrane phospholipid metabolism which facilitate the influx for excitation-calcium - an event which is obligatory for excitation-secretion coupling and thereby preceeds the onset of mediator release.

Chakraborty and Yu (1986) proposed that calcium (Ca) has a dual role on histamine release from mast cells. Increased calcium concentration in the cytosol act as the second messenger and initiate the secretory process. Calcium also has a regulatory
function on histamine secretion. The inhibitory effect of extracellular calcium on histamine secretion has been demonstrated using low concentration of compound 48/80. The effect is enhanced by higher pH, probably because of a stronger binding of calcium to the regulatory sites in the plasma membrane at this pH.

Yoshii et al (1991) revealed by means of the Ca-antimonate precipitation technique that calcium accumulates in the endoplasmic reticulum (ER) of rat peritoneal mast cell and ATP is necessary to retain calcium in the ER. Inositol 1,4,5 triphosphate and GTP (guanosine triphosphates) was effective in releasing calcium from the ER. This may indicate that a hydrolysis of GTP is necessary for calcium release from the ER.

Hinson et al (1989) said that mast cells were present in the rat adrenal gland. The mast cell products such as histamine and serotonin both caused dose dependent increases in rates of flow of perfusion medium and steroid secretion in the isolated perfused rat adrenal gland in sites. Compound 48/80, a mast cell degranulator, caused a significant increase in perfusion medium flow rate and steroid secretion.
Hirano (1989) found that the mast cell or basophil degranulation and release of chemical mediators such as histamine from rat peritoneal mast cells (RPMC) by compound 48/80, kallikrein or peptidoglycan was modulated or regulated by cAMP content of RPMC.

The survival of mast cells in higher organisms seems to imply that they have some vital physiological functions, possibly concerned with cardiovascular homeostasis by releasing various vasoactive and chemotatic principles, which are stored in an active form at acidic pH inside the secretory granules (Schwartz, L.B., 1994).
Histamine

The name "histamine" has been derived from Greek word 'histolog' meaning 'tissue'. Histamine or \( \beta \)-aminoethylimidazole was first extracted from ergot as a uterine stimulant. In 1927 Best, Dale, Dudley and Thorps isolated histamine from lung and liver tissue, thereby establishing histamine as a natural constituent of the body. That gastric mucosal cells are the sources of histamine responsible for stimulation of oxyntic cells had been proposed by Rasenenn (1969).

Riley and West (1953) first proposed a positive correlation between the mast cell population and histamine concentration of the tissues and it was observed that a tissue having more mast cell population contains high concentration of histamine whereas tissues with less number of mast cells contain low histamine concentration. Several investigators described the presence of mast cells in perivascular tissues as found in lung, spleen, intestine, skin, liver etc. (Parratt and West 1957, and Hunaeu et al 1989).
Dale and Laidlaw (1910) first discovered that histamine has vasodepressor effect. Several reports suggest that histamine has a biphasic and dual role on blood pressure - a constrictor action on large arteries and a more peripheral dilator effect on the capillaries. It has been observed that the effect of histamine on blood pressure is dependent on the balance between its constrictor action on large vessels and its dilator action on capillaries (Dale and Laidlaw, 1919; Feldberg, 1927).

May et al (1988) found that hypertension induced by intravenous administration of morphine in conscious rabbits was enhanced by pretreatment with antihistamines like cimetidine and chlorpheniramine.

Lüscher (1994) demonstrated that histamine played its dilator action by the activation of the protective metabolic process in the endothelium.

Some cell products are capable of interacting with mast cells or basophils and causes histamine release. These histamine releasing factors are
products of platelets, neutrophils, alveolar macrophages and mononuclear cells like T-lymphocyte, B-lymphocyte and monocytes (Kaplan et al, 1991).

Folkow et al (1948) had suspected that histamine acts through more than one receptor and now it is clear that three distinct subclasses of receptors exists.

a) $H_1$ receptor mediates the edema and vascular effects of histamine (Ash, and Schild, 1966). Vigorito (1988) reported that histamine induces a direct $H_1$ receptor mediated peripheral coronary vasodilatation in patients with normal coronary arteries.

Binding studies with mepyramine have revealed that presence of a large number of histamine $H_1$ receptors in the cardiac myocytes and the data have suggested that histamine acted by altering the availability of calcium for $\alpha_1$-mediated activation of cAMP phosphodiesterase within the myocytes (Buxton, 1986).

showed that histamine stimulates formation of endogenous cAMP which in turn activates the cAMP dependent protein kinase activity and has been implicated as the first step in a series of reactions culminating in the stimulation of gastric acid secretion.

Tsunema and Yutaka (1985) suggested that histamine may induce or enhance the delayed after depolarisation and triggered activity by increasing the slow inward current. This mechanism may be mediated by histamine H₂ receptor and the adenylate cyclase system in the cardiac ventricular muscle. Lukovic and Machova in 1988 also supported the ganglionic depolarising action of histamine.

c) H₃ receptors are located in the brain, the exact role of which needs exploration (Hey, 1992). Poli et al (1991) suggest that intestinal cholinergic nerves are endowed with histamine H₃ receptors whose activation produces an inhibitory effects on acetylcholine release.

Halonen et al (1984) found that histamine induced several graded alterations including an increase
in total pulmonary resistance, a decrease in dynamic compliance, a rise in right ventricular systolic pressure and systemic hypotension. Inhibition of the histamine - induced systemic hypotension require pre-treatment with both $H_1$ & $H_2$ histamine antagonists.

Some investigators demonstrate that histamine produces a transient and rapid rise in blood pressure by causing depletion of epinephrine from the adrenals and it was interpreted that pressor response of histamine is mediated by release of endogenous epinephrine (Naranjo and Naranjo, 1958).

Other investigators found that histamine increases the re-uptake of noradrenaline in presynaptic neurone. Antagonists of $H_1$ receptor has been reported to block the entry of amines in the sympathetic nerve ending lead to increased synaptic concentration of the amine (Alhaider and Mustafa, 1989).

Ennis & Pearce (1980) also showed that adrenaline inhibits the Ach evoked histamine release from isolated purified rat mast cells. The inhibitory effect of adrenaline is reversed by pre-incubating the cells with a $\beta$ - blocker, alprenolol, but not by pre-incubating them with an $\alpha_1$ blocker, phentolamine.
Diamine oxidase (DAO) or histaminase is found in various perivascular tissues and is pre-eminent in histamine catabolism (Lorenz et al., 1971; Disiderio et al., 1982; Kusche et al., 1987).

Huneau et al. (1989) suggested that DAO is located outside the mast cell and histamine must first be released before being processed by this enzyme.

Serotonin:

Serotonin or 5-hydroxytryptamine (5-HT) is biosynthesized from L-tryptophan via hydroxylation and subsequent decarboxylation. Serotonin was first isolated by Vittorio Erspamer in 1940 and identified as a vasoconstricting agent in serum from clotted blood (Rapport, 1949). Benditt et al. (1955) found that serotonin may associate with mast cell. In 1957, Parratt and West described the occurrence of 5-HT in different tissues of mammals and its relationship to tissue mast cells and histamine. Erspamer in 1954 obtained in spleen of different species high concentrations of 5-HT. Garven (1956) obtained 5HT from mast cell extraction.
Several reports suggest that serotonin is predominantly found in enterochromaffin cells, platelets, neurons, blood vessels and in mast cells of different perivascular tissues present in lung, liver, spleen etc. (Chiravat 1970; van Zwieten et al, 1990; Chandra and Chandra, 1993). Nearly all the serotonin released is inactivated by liver or pulmonary endothelial cells (Thompson, 1971, Strum and Junod, 1972). The remaining part is either taken up and stored by nonaggregating platelets or taken up and metabolised in endothelial cells. van Houtte (1991) demonstrated that part of the circulating serotonin is taken up and stored by the platelets, when the platelets aggregate the released serotonin feeds back on the platelets to amplify the coagulation process. This amplification can be blocked with 5-hydroxytryptamine antagonists. Serotonin is taken up and destroyed by the endothelial cells, these cells also release endothelium derived relaxing factors (EDRF) when exposed to the monoamine. The release of EDRF evoked by serotonin is not prevented by 5-hydroxytryptamine-2, serotonergic receptor antagonists and involves a pertussis toxin sensitive G-protein. When serotonin reaches vascular smooth muscle, it usually causes it to contract. This in most blood vessels, is prevented by 5 HT-2 serotonergic antagonists.
Page (1954) first assumed that serotonin might play a regulatory role in hypertensive disease. Serotonin after its release by activation of mast cells generally constricts arteries and veins. Serotonin causes vasodilation 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). Gillis et al (1988) also suggested that serotonin effects are complex and activation of one type of receptors (presumably $S_2$) results in increase of blood pressure and heart rate, while activation of another type of receptor (presumably $S_1$) results in a decrease in arterial blood pressure and heart rate.

The past decade had been important progress in understanding the localization, pharmacology and function of serotonin receptor subtypes, serotonin acts by interacting with receptors on the cell membrane. Gaddum and Picarelli (1957) first classified these serotonergic receptors as D and M type. Three major classes have been recognised by using radiologic and binding techniques (Bradley et al, 1986). (1) $S_1$ receptors are present in smooth muscle,
peripheral and central neurons. These receptors mediate prejunctional inhibition of neuronal transmitter release, smooth muscle relaxation etc. (ii) $S_2$ receptors situated in vascular smooth muscles, cardiac pacemaker cells, platelet, bronchi, adrenal cortex, central and peripheral neurones etc mediate gastrointestinal and vascular smooth muscle contraction, platelet aggregation, neuronal depolarization etc.

(iii) $S_3$ receptors situated in central and peripheral neurones mediate depolarization of the neurones (Chandra & Chandra, 1993). The exact role of $S_3$ receptor needs to be explored.

Saxena et al (1987) reported that peripheral 5-HT elicits vasodilation (both directly and indirectly by release of vasodilator substances from endothelium) or vasoconstriction (associated with amplification or noradrenaline response) or mainly "large" conductance arteries mediated by 5-HT-2 receptor.

Nityanand et al (1989) said that in essential hypertension, the reduced uptake of serotonin by blood platelets causes an increase in circulating serotonin level which could result in an increased serotonin concentration at sites like heart and blood vessel walls where $S_2$ receptors are situated.
Pergola and Alper (1991) reported that 5-HT injected into the lateral cerebral ventricle of conscious rats induces sympatho-excitation and release of vasopressin, which results in an increase in mean arterial pressure. This increase in mean arterial pressure produced by 5-hydroxy tryptamine was potentiated by chlorisondamine (a ganglionic antagonist).

Collis et al (1979) surmised that 5-HT may potentiate the release of norepinephrine and angiotensin II. This is further supported by Myers et al (1985).

Fuder et al (1994) demonstrated that serotonin receptors 5HT-3 or 5HT-4 subtypes are known to facilitate acetylcholine release upon compound 48/80 exposure. Such prejunctional influences of immunological mediators may contribute to cardiac dysfunction by induction of imbalance of autonomic neurotransmission. Dragsted and Boeck (1988) also reported that irindaline, a peripheral 5HT-2 antagonist has an antihypertensive effects.
**Heparin**

Heparin was discovered by McLean in 1916. Holmgren and Wilander (1932) first noticed the association of heparin with mast cells. It is a naturally occurring substance found in association with lipoproteins in the secretory granules of the mast cells. Heparin is mucopolysaccharide composed of D-glucoronic acid and N-acetyl D-glucosamine residues (Lindahl et al, 1986). Heparin is mainly metabolised by the liver and is partially taken up by the reticulo-endothelial system of the body.

Heparin sulphate molecules present on the luminal surface of vascular endothelial cells interact with circulating antithrombin to provide a natural antithrombotic mechanism. (Fitz Gerald et al. 1967; Rock et al. 1970; Engelberg, 1975).

Susic et al (1982) reported that heparin lowered the blood pressure in rats with developed Goldblatt's hypertension. Heparin causes a significant increase in cardiac output and a significant decrease in total peripheral resistance and packed cell volume.
The blood pressure lowering effect of heparin may be attributed to a decrease in packed cell volume.

Hales et al (1983) demonstrated that chronic hypoxia produces pulmonary artery hypertension and high dose heparin partially but significantly prevented the pulmonary artery hypertension.

Chronic hypoxia produces pulmonary hypertension and an increase in medial thickness of pulmonary arteries that reach maximal values after 10 days of hypoxia. In guineapig, heparin given during the first 10 days of hypoxia reduced the development of both pulmonary hypertension and vascular remodelling. Heparin reduced total pulmonary resistance increased with hypoxia (Hassoun et al, 1992).

Heparin inhibits smooth muscle cell growth in vitro and inhibits the development of hypoxic pulmonary hypertension and vascular remodelling invivo. (Thompson et al, 1994).

Vasdev et al (1992) surmised that oral heparin treatment normalized the elevated platelet, cytosolic free calcium, aortic calcium uptake and systolic blood
pressure in spontaneously hypertensive rats but had no effect on Wister-Kyoto rats. Heparin also prevented onset of adverse renal vascular changes observed in spontaneously hypertensive rats. Oral heparin treatment did not cause abnormal, hematological, biochemical or pathological changes in rats.

Vasdev et al (1994) also revealed that increase calcium uptake in vascular tissue leading to elevated cytosolic free calcium has been implicated in the pathogenesis of hypertension. High dose Low molecular weight heparin normalized 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. Oral low molecular weight heparin did not cause any abnormal hemotological, biochemical or pathological changes in rat.

Intravenous injection of heparin is promptly followed by marked rise of plasma diamine oxidase (DAO) level. There was an inverse correlation between the serum glutamic pyruvic transaminase (SGPT) and the post-heparin enzyme. Normalisation of SGPT occured before the normalisation of post-heparin diamine oxidase (Gang et al, 1976).
Wolvekamp and de Bruin (1994) reported that after intravenous administration of heparin DAO is released from its capillary binding site in the lamina propria into the peripheral circulation.

Noradrenaline

Noradrenaline (NE) is a peripheral neurotransmitter. Synthesis of noradrenaline starts with conversion of L-tyrosine to L-3,4 dihydroxy phenylalanine (L-DOPA). This step of reaction is catalysed by the enzyme tyrosine hydroxylase which has a narrow substrate specificity and which is the overall rate limiting step. L-DOPA is then decarboxylated to Dopamine with the help of the enzyme amino acid decarboxylase. This enzyme has substrate specificity for L-isomers in preference to D-isomer. It too has affinity for other substrates like L-Methyl DOPA and thereby converted to L-methyl dopamine. This enzyme is inhibited by carbidopa which acts mainly in peripheral tissues and by benserazide, acting both centrally and peripherally. The final step is the conversion of dopamine to noradrenaline by dopamine beta-hydroxylase, located mainly on the membrane storage granules. Noradrenaline can be converted to adrenaline by phenylethanolamine N-methyl transferase.
The synthesised catecholamines are stored in the storage granules which are present in the nerve endings (Carlsson et al, 1962). Released catecholamines are subsequently inactivated by reuptake, metabolism or diffusion from the synaptic cleft. Degradation of the catecholamines occurs with the help of monoamine oxidase (MAO) and catechol-o-methyl transferase (COMT). COMT is present in most cells and functions extraneurally, whereas MAO is largely localised in the mitochondria of the neurone. Reuptake of catecholamines by the nerve endings can be inhibited by tricyclic antidepressant.

Electrical stimulation of the hypothalamus of rats and cats causes a rise in blood pressure while electrical stimulation of various hypothalamic nuclei enhances release of catecholamines from the cat hypothalamus (Philippu et al, 1971). Therefore NE released from nerve endings of the brain may contribute to the regulation of systemic blood pressure.

In experimentally produced neurogenic hypertension, it has been found that the increased blood pressure is associated with and dependent on an increased turnover of NE in bulbospinal catecholaminergic nerves (Chalmers, 1975).
A marked increase in systemic blood pressure was seen in patients after infiltration with 15 to 20 ml of 0.5% lignocaine with noradrenaline 1 μg/ml. In control series, when saline injected, a slight fall in blood pressure was registered. (Christensen et al, 1980).

Collis et al (1979) found that the contractile action of noradrenaline is potentiated by serotonin. This sensitizing action of serotonin is mediated by the activation of the S2 - serotonergic receptors.

In essential hypertension, treatment with labetolol causes a reduced elimination of nonadrenaline from plasma and thereby a increased pressor response is maintained (Zschiedrich et al 1983). Banks in 1988 reported that norepinephrine releases histamine and prostaglandins from the kidney and the prostaglandins account primarily for norepinephrine reactive hyperemia.

Some investigators found that histamine increases the reuptake of noradrenaline in the presynaptic neuron. Antagonists of H1 receptor has been reported to block the entry of amines in the sympathetic nerve endings leading to increased synaptic concentration of the amine (Alhaider. and Mustafa, 1989).
Noradrenaline raises blood pressure by constricting the arterioles and so raising the total peripheral resistance with reduced blood flow. Though it does have slight cardiac stimulant effect, the tachycardia of this is masked by the profound reflex bradycardia caused by the hypertension. (Laurence and Bennett, 1992).

Intravenous administration of noradrenaline causing marked venoconstriction contributes to the increased resistance. Norepinephrine constricts mesenteric, renal, splanchnic and hepatic vessels and thereby reduces blood flow. Coronary flow is substantially increased, probably due to indirectly induced coronary dilation as with epinephrine and elevated blood pressure. (Hoffman & Leftowitz, 1991).

Choi et al. 1993 demonstrated that histamine stimulated inositol monophosphate accumulation in epinephrine containing chromaffin cells was three times greater than norepinephrine containing chromaffin cells and histamine stimulated catecholamine secretion also greater in epinephrine cells than in norepinephrine cells. The density of $H_1$ receptor in epinephrine-cells is three times greater than norepinephrine cells.
Greater density of $H_1$ receptor may account for the greater effects of histamine on inositol monophosphate accumulation and catecholamine secretion in these cells.

Fuder et al (1994) elucidated that release of mediators upon mast cell degranulation in the heart is accompanied by a complex pre-junctional modulation of autonomic neurotransmitter release, Noradrenaline release may be inhibited by a serotonergic mechanism involving 5 HT$_2$ receptor sub-type.