

## MAST CELLS, VASOACTIVE INTESTINAL PEPTIDE (VIP), AND THE HEMORRHAGIC SHOCK: A POSSIBLE RELATIONSHIP?

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### SUMMARY

• *The key mechanisms associated with irreversible hemorrhagic shock have not so far been elucidated. The involvement of mast cells in this phenomenon, however, has already been studied. On the other hand,  $\beta$ -endorphine and various opiates, or any stressful stimuli mediated by endogenous opiates, cause mast cell degranulation and histamine release, as the study of the related literature shows. Hemorrhagic shock is one such stressful stimulus that leads to an increase in the plasma levels of endogenous opioids, especially  $\beta$ -endorphine. During hemorrhagic shock, therefore, mast cells can be activated by an elevation of the  $\beta$ -endorphine level; and the degranulated products of mast cells, histamine in particular, may contribute to the progress of hemorrhagic shock to the irreversible state.*

*The investigation of the effect of hemorrhage on mast cell degranulation has shown that there is a positive correlation between the two phenomena. In addition, it has been established that the administration of vasoactive intestinal peptide (VIP) prevents such degranulation. Depending on these results, the effects of VIP have been studied in the treatment of severe experimental hemorrhagic shock in combination with other therapeutic means used in this type of shock, such as naloxone, hypertonic saline infusion and/or blood reperfusion. A combination of VIP and naloxone has yielded the best results on survival when it is used either alone or in conjunction with volume replacement after a severe hemorrhage.*

*The important prospect of a combination of VIP and naloxone is that it has apparently the most potent inhibitory effect on mast cell degranulation. In the light of the related experiments, we may conclude that the inhibition of mast cell degranulation has a beneficial effect on severe hemorrhagic shock; mast cell degranulation may thus be accepted as a physiopathological mechanism contributing to the progression of hemorrhagic shock state.*

### INTRODUCTION

• Hemorrhagic shock which is the most common type of shock encountered in clinical medicine, appears to be dependent on various conditions. Depending largely upon the amount of blood lost, it can progress into different stages from the compensated to the irreversible state. In the irreversible state, the shock progresses to a point which any therapeutic approach will be inadequate to save the life of the afflicted person. There has been much discussion about what makes shock irreversible (1). It is known that a number of deleterious positive feedback mechanisms become operative; nevertheless, the key mechanisms associated with this stage have not been elucidated as yet (2,3). Therefore the question remains, What factor or factors lead to the eventual deterioration of microcirculation? Investigations have been focused to elucidate the physiopathologic mechanisms which may have

a role in the disruption of microcirculation. With a better understanding of the physiopathologic mechanisms involved in irreversible shock, more and more patients can obviously be saved and treatment strategies may be improved.

Production of eicosanoids, especially of thromboxan  $A^2$  (4,5), the release of myocardial depressant factor from intestine (6), generation of free oxygen radicals (7,8), plugging of white blood cells and thrombocytes in the capillary (2,9,10), swollen endothelial cells (11), activation of lysosomal enzymes (12,13), and the waning of hyperglycemia (14) are claimed to be closely associated with the progressive deterioration of microcirculatory homeostasis during hemorrhagic shock.

After the discovery of endogenous opioid, as well as their receptors, a new insight has arisen as regards the mechanism of hemorrhagic shock (15,16). In 1978 Holaday and Faden proposed that endogenous opioids (endorphins) were major factors contributing to the physiopathology of shock (17). Experiments with opioid antagonists have revealed that endogenous opioid system within the central nervous system (CNS) are activated by stressful situations such as hemorrhagic shock (15,16,18). During hemorrhagic shock plasma levels of endogenous opioids, especially of p-endorphine, increase and contribute to the loss of circulatory homeostasis (15,19,20). In general, this may involve in an inhibition of sympathetic outflow, and perhaps an augmentation of parasympathetic tone (15,20,21,22).

On the other hand, endogenous opiates have another effect that could be partly responsible for the physiopathology observed in this form of shock, p-endorphine and various opiates or any stressful stimuli mediated by endogenous opiates cause mast cell degranulation and histamine release (23,24,25). Mast cell - derived histamine is believed to contribute to the disruption of cardiovascular function (15,20,26). During hemorrhage, therefore, mast cells can be activated by elevated p-endorphine and degranulated products of mast cells, among which histamine in particular, may be involved in the progress of hemorrhagic shock to irreversible state (26,27).

## MAST CELLS

- Granulated mast cells, the major source of the body's histamine, originate from the bone marrow. They are ordinarily distributed throughout the normal connective tissue, where they are often situated adjacent to blood vessels and lymphatics, and beneath epithelial surfaces those of the respiratory and gastrointestinal system and

the skin (28). They are also localised in the CNS (29,30), sympathetic ganglia (31) and close to the intestinal peptidergic nerves (32). The function of mast cells which are close to the neurons is not yet clear. However, they possibly have modulatory effect on nerve activity (32,33). In addition, under physiological conditions a considerable amount of brain histamine is located in mast cells (30,33,34). Mast cells from different locations are shown to vary in their histochemical, ultrastructural, cytochemical and functional properties. Depending on their heterogeneity, they are categorized as mucosal and connective tissue or typical and atypical mast cells (28,35). However, because of the insufficiency of the nomenclature in the recognition of the full extent of mast cell heterogeneity, this type of classification has not yet been widely accepted (36,37).

Mast cell granules contain different kinds of substances such as histamine, heparin, slow reacting substance of anaphylaxis (SRS-A), eosinophil chemotactic factor of anaphylaxis (ECF-A), bradykinin, prostaglandins, leukotrienes, nitric-oxide-like factor, and vasoactive intestinal peptide (VIP). or closely related peptide (35,38-39,40,41).

Histamine is known to be the major functional product of these cells. Mast cell-derived histamine has been implicated in the regulation of the immune system (42), modulation of the synaptic transmission (31), tissue growth and repair (43); thus, it is not simply a vasoactive amine.

Stimulation of mast cells cause degranulation and release of the granular products, especially histamine. Activated mast cells have some role in the regulation of various biologic responses and diseases (28). However, explanation of their specific roles in health and disease needs yet to be elucidated.

Degranulation of mast cells may be included in response to a wide variety of substances other than IgE (44, 45). As mentioned above, one of the agents that cause mast cell degranulation is opioid peptides. There are numerous studies which confirm the capacity of these agents to cause mast cell degranulation (23,26,46,47,48). Therefore, mast cell degranulation during the hemorrhage is possibly the consequence of the elevated p-endorphins.

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## THE EFFECT OF HEMORRHAGE ON MAST CELL DEGRANULATION

- In our first study, we observed that hemorrhage caused mast cell degranulation in rats in correlation with the amount of blood loss (49). The most intense degranu-

lation was observed in the hypothalamus, especially in the nucleus arcuatus, and in the subcutaneous tissue. The granules of the hypothalamic mast cells were found to be larger than those in other types of tissue. The number, histamine content and exocytosis of mast cells, on the other hand, were highest in the subcutaneous tissue. The intensity of degranulation gradually decreased in the peripheral blood vessels, peritoneum and omentum, respectively. While there is a decreasing gradient in degranulation from subcutaneous tissue to the omentum, an increase in the number and histamine content of mast cells was found to be almost equal in two tissues, namely the peripheral blood vessels and the omentum. In this way, the hypothalamus and subcutaneous tissue could be accepted as indicator tissues for the determination of the intensity of degranulation. The most intense mast cell degranulation, i.e., that in the arcuate nucleus of hypothalamus, is possibly related to the (3-endorphine secreting neurons localized in this area (20). During stressful situations such as hemorrhage, (3-endorphine is released by these neurons either into the hypothalamus or into the blood stream, and binds opioid receptors on the surface of mast cells, thus causing degranulation and histamine release (20,26). In 1986 Nagy et al. observed a rapid, severalfold increase of plasma and tissue histamine on both conscious and anaesthetized dogs subjected to experimental hemorrhagic shock; they reported that the source of the elevated histamine was unknown (50). Correlating our results with Nagy's findings, we can conclude that degranulated mast cells might be the source of the histamine elevation during hemorrhage shock.

#### **THE SIGNIFICANCE OF MAST CELL DEGRANULATION DURING HEMORRHAGE**

- The question now arises, why do mast cells degranulate in hemorrhage? For the benefit? Or is this phenomenon to be considered as a harmful reaction? It is possible that initially it is an essentially beneficial reaction, but that later on, when in excess, it becomes a deleterious phenomenon.

Both, mast cell-derived histamine and p-endorphine, have been accepted as defensive mediators of the body to react to stressful stimuli (51,52), and the brain histamine turn over is increased by stress (28,52). Histamine is known to stimulate the release of ACTH (27,52). The amount of ACTH secretion is enhanced to meet the emergency situation during stress and its release is mediated almost exclusively through the hypothalamus. Either i.c.v. administration of histamine (53) or degranulation of brain mast cells by compound 48/80 (54) stimulates the pituitary-adrenocortical activity. Therefore, mast cells located in the hypo-

thalamus may serve as "emergency cells" when the body needs more histamine secretion.

In addition to its stimulatory effect on ACTH, histamine evokes an increase in plasma ADH level when administered peripherally or centrally (33,55). Therefore, a speculative suggestion can be derived that even without a change in the osmolality of plasma, mast cell-derived histamine may be another responsible stimulator of ADH during hemorrhage. In hemorrhagic shock the beneficial effect of histamine elevation was implied by Nagy et al. (50). Subjecting animals to moderate hemorrhage, higher survival rates were observed in the groups displaying higher plasma histamine levels and a higher ratio of histamine to norepinephrine and renin. As a powerful vasodilator agent, counterbalancing the excessive effect of vasoconstrictor agents, histamine could be a significant factor for survival (50,56).

All the compensatory responses mentioned above which are initiated by histamine may turn out to be harmful to the body when histamine release or mast cell degranulation is excessive and/or prolonged. In a condition such as hemorrhage in which the intensity of mast cell degranulation gradually increases in correlation with the amount of blood loss, gradual histamine elevation and occurrence of the deleterious effect of histamine (57,58,59) must be expected. For this reason, when the insult is excessive, a modulatory mechanism may be expected to act to limit the degranulation involved.

#### **VASOACTIVE INTESTINAL PEPTIDE (VIP) AS A MODULATORY AGENT FOR MAST CELL DEGRANULATION**

- Vasoactive intestinal peptide (VIP) is a basic peptide of 28 amino acid residues which was originally identified in the gastrointestinal tract by Said and Mutt (60). Like various other peptides of the gastrointestinal or of endocrine origin, VIP is also present in the nervous system, its highest concentration (61,62,63) as well as that of histaminergic neurons (64,65) being found in the hypothalamus. VIP is also found in mast cells together with histamine, and from where it can be released by histamine releasers (40,41). A conclusion may now be drawn that VIP is to be found wherever histamine is present. It has been supposed that the VIP localized in mast cell has some modulatory effect on degranulation and mediator release from mast cells (40,41). VIP increases the intracellular c-AMP levels by activating adenylate cyclase (66,67). A decrease in c-AMP levels in mast cells stimulates the degranulation (36,38). Thus, possibly, inhibiting the release of mediators from mast cells through the increase in c-AMP mechanism, VIP may have an important modulat-

ing effect on the degranulation and Histamine release.

The inhibitory effect of VIP on mast cell degranulation was observed in our first experimental hemorrhagic shock model (49). In this experiment, the effects of VIP, H<sub>1</sub> and H<sub>2</sub> receptor blockers and aprotinin on mast cell degranulation were investigated in rats exposed to hemorrhage. Degranulation was prevented by VIP in a dose dependent manner and 25 ng kg<sup>-1</sup> dose of VIP potentially inhibits the degranulation. On the other hand, H<sub>1</sub> and H<sub>2</sub> receptor blockers and aprotinin have no inhibitory effect. These data seem to support the suggestion that VIP has a modulatory effect on histamine and other mediator release from mast cells.

A relationship between VIP and histamine was observed in one of our earlier studies unrelated to hemorrhagic shock (25). In this experiment, exposure of guinea-pigs to stress (immobilization in cold for one hour and swimming thereafter) caused degranulation and increased the number of mast cells in trachea. Contractile responses of isolated tracheal strips of stress-induced groups to both histamine and acetylcholine (ACh) were higher than the control. While the most relaxing effect of VIP occurred in the stress-induced strips precontracted by histamine, there was no relaxing effect of VIP to ACh contraction. These data were somewhat confirmatory to the suggestion about the modulatory effect of VIP in the release of histamine and other mediators from pulmonary mast cells (41,69). Therefore, in any conditions that cause mast cell degranulation, VIP may exert its relaxant action on bronchial smooth muscle by inhibiting histamine contractions.

It is possible that these findings will lead to a new preventive and/or therapeutic application in hemorrhagic shock. Combination of VIP with the other therapeutic interventions used in the treatment of hemorrhagic shock may have a beneficial effect by modulating mast cell degranulation. In addition, VIP has a favourable effect also on cardiovascular system via its systemic vasodilator and positive inotropic action (70,71). Therefore, either by modulating mast cell degranulation or through its cardiovascular effects, VIP seems to be a good candidate as a therapeutic agent in the treatment of hemorrhagic shock.

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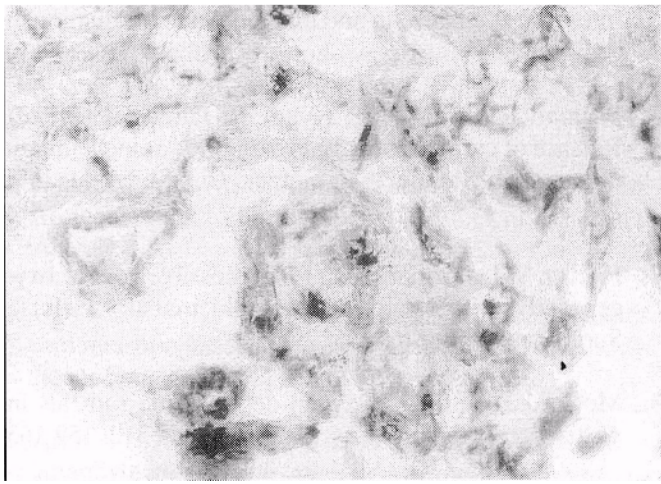
#### **VIP IN THE TREATMENT OF SEVERE EXPERIMENTAL HEMORRHAGIC SHOCK**

- Hemorrhagic shock treatment primarily consists of fluid replacement. However, restoration of blood volume does not always result in successful recovery. Microcirculatory disruption developing through various mechanisms may cause reduced reflow or no-reflow in the

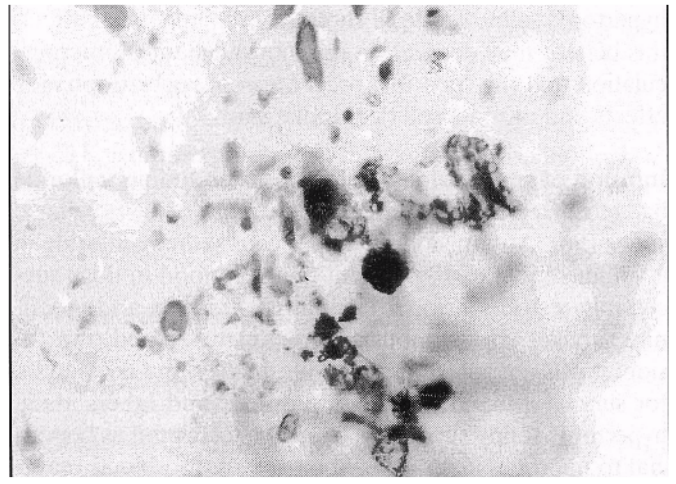
capillary bed even after systemic circulatory function was restored (2,3). Furthermore, restoration of flow to previously ischemic tissues may trigger reperfusion injury which may result in increased tissue damage (8,72). For this reason, investigation has been focused to find the suitable agents that would be beneficial for microcirculation during hemorrhagic shock. Depending on the generation of free oxygen radicals involved here, some investigators studied the prevention of oxygen-derived free radical injury in hemorrhagic shock (73,74). In these experiments, allopurinol (a xanthine oxidase inhibitor) substantially increased the survival rate of dogs subjected to hemorrhagic shock. Pentoxifylline is another agent used in the treatment of various kinds of shock including hemorrhagic shock (75). Waxman et al. have reported that pentoxifylline improves survival when used in addition to fluid replacement (76). Despite several questions remaining unanswered concerning pentoxifylline, it is claimed that it has significant hemorrheologic effects (77). Pentoxifylline decreases leukocyte (78,79) and thrombocyte (80) aggregation, increases deformability of normal red cells (77), and improves the microcirculatory blood flow and tissue oxygenation (75,76).

On the basis of increased endogenous opioids during hemorrhagic shock, treatments were directed to block the effect of opiates. For this purpose, naloxone (81,82), TRH (83) and some antiserotonergic agents were used (84). The most widely used agent has been naloxone (15,20,83). Being a synthetic broad spectrum opioid receptor antagonist, naloxone competes with naturally occurring opioids and blocks their effects. With reference to the mechanism for the favourable action of naloxone in the treatment of hemorrhagic shock, emphasis has been placed on the observation that the drug increases sympathetic nerve activity (15,20,81,83), improves myocardial contractility (81,85,86), suppresses the release of lysosomal enzymes (12,13) and myocardial depressant factor (12,13), increases blood pressure (82,87,88,89) and cardiac output (82,90), improves the microcirculation and tissue metabolism (3,12), and leads to an increase in survival rates (12,15,88). However, and depending on some controversial data, the effect of naloxone on both hemodynamics and the long-term survival of experimental animals exposed to severe hemorrhage is not significantly higher or even clear (91,92,93).

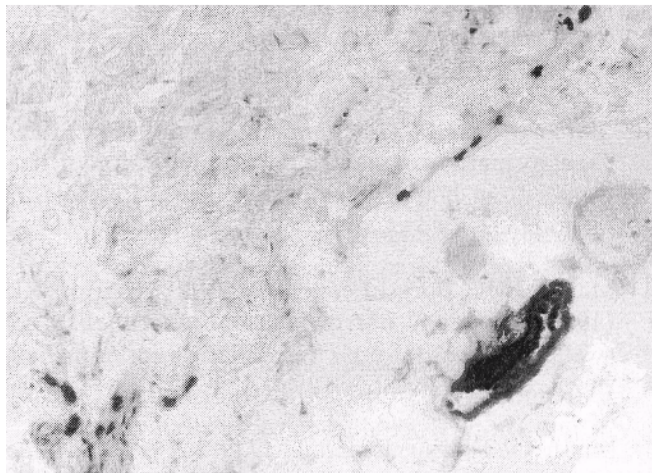
Because the key mechanisms associated with irreversible hemorrhagic shock have not been elucidated sufficiently, and because there is insufficient improvement in the survival with the use of naloxone alone, the prevention of mast cell degranulation by the administration of VIP, in addition to the blockade of the opioid receptors by naloxone,



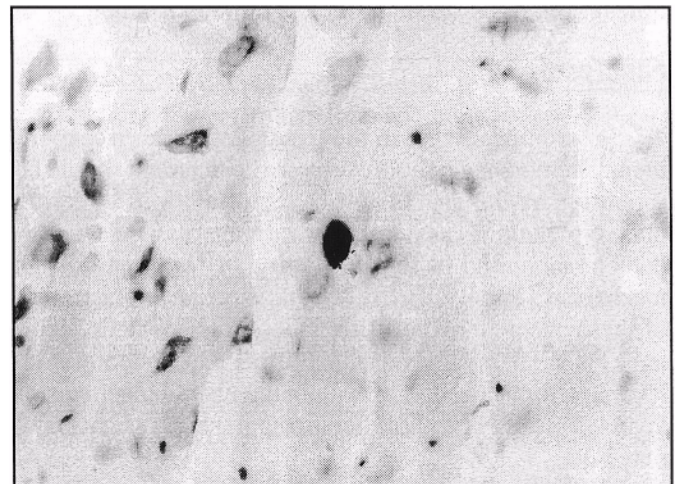
(a)



(b)



(c)



(d)

Figure 1.

Mast cells degranulation in 40 % decrease of circulating blood volume: (a) Subcutaneous tissue (toluidine blue x 20 x 3.3), (b) Hypothalamus (toluidine blue x 40 x 3.3), and the prevention of that degranulation by a VIP and naloxone combination: (c) Subcutaneous tissue (toluidine blue x 20 x 3.3), (d) Hypothalamus (toluidine blue x 40 x 3.3).

may improve the survival rate in severe hemorrhagic shock. Accordingly, varying doses of VIP was combined with varying doses of naloxone in our more recent study, and those combinations were used either alone or in conjunction with fluids in the treatment of severe hemorrhagic shock model in rats (94). In this experiment, a combination of 25 ng kg<sup>-1</sup> VIP + 5 mg kg<sup>-1</sup> naloxone showed the best results on survival when used alone after hemorrhage of the 40 percent of the total blood volume. The importance of this combination is that it has apparently the most potent inhibitory effect on mast cell degranulation (Fig. 1 a,b,c,d). When this combination was given together with shed blood reperfusion or 7.5% NaCl, survival rate increased relative to the administration of shed blood and of 7.5% NaCl alone. These findings suggest that inhibition of mast cell degranulation

in addition to the volume replacement seems to be beneficial. Mast cell degranulation may thus be accepted as a pathophysiological mechanism contributing to the progression of the hemorrhagic shock state. In addition, it was observed in this experiment that blood reperfusion has no superiority over hypertonic saline treatment. This may be explained by the reperfusion injury which may develop during blood reperfusion (72,95). Recent evidence suggests that additional cellular injury can result during reperfusion of previously hypoxic tissue. The mechanisms of reperfusion injury are complex and hypothetically dependent on the formation of excess free oxygen radicals resulting from cellular calcium alteration, on the aggregation of thrombocytes and leukocytes, and on thrombus formation (9,72). The addition of a VIP-naloxone combination either in

hypertonic saline or blood showed some beneficial effect; this benefit may depend on the improvement of microcirculation and the possible prevention of reperfusion side effects and of mast cell degranulation.

Infusion of small volumes of hypertonic sodium chloride has recently been used for the treatment of hemorrhagic shock (96). An infusion of 7.5 per cent sodium chloride in a volume equal to, 10 per cent of shed blood in dogs successfully restored normal circulatory function and indefinite survival time without accompanying blood transfusion; it was proposed that high plasma sodium is essential for survival (96,97). Depending on our and others' data, hypertonic saline supported by agents accepted as beneficial to microcirculation may be preferred to blood reperfusion in the treatment of severe hemorrhagic shock. Such therapeutic modality avoids the adverse effects of blood transfusion, easier to find and less time-consuming.

## CONCLUSION

- It appears that in the treatment of severe experimental hemorrhagic shock, volume replacement should be supported by the agents that have a salubrious effect on microcirculation. The number of such agents would apparently be increased by the elucidation of physiopathologic mechanisms involved in irreversible shock. Administration of these agents together with volume replacement seems to be essential for survival gain. Further experimental studies are certainly needed to explain the overall mechanisms involved in the irreversible hemorrhagic shock with its fatal outcome.

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