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Review Article

Perioperative Anaphylaxis and Chronic Inflammatory Diseases: The Role of Mast Cells

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ABSTRACT

Aim of review: To provide a brief overview of the perioperative anaphylaxis and inflammation role of mast cells.

Methods: We searched the keywords "inflammation" or "anaphylaxis" or "perioperation" combined with "mast cells" in the Pubmed. A current review of original studies, systematic reviews, and meta-analysis within the past decade were included in the analysis.

Recent findings: Mast cells are observed around blood vessels in most tissues, therefore making them well-positioned to react quickly to internal and external environmental threats (stimuli). Mast cells are important in the regulation of the neuro-endocrine-immune network. Mast cells and their secreted mediators participate in a variety of physiological and pathological processes, such as perioperative anaphylaxis and central nervous system (CNS) inflammatory processes. In recent years, it has been recognized that mast cells are not only related to anaphylaxis, but also involved in the occurrence and development of acute central nervous inflammation after the operation.

Summary: The MCs play a key role in regulating normal physiological processes and many pathological conditions. The degranulation of mast cells could induce the anaphylaxis and inflammation. However, mast cells degranulation is unpredictable, so that the main concern is the avoidance of release of histamine and other MC mediators and the management of risks induced by mast cells. (Funded by the National Natural Science Foundation of China, Postgraduate Research & Practice Innovation Program of Jiangsu Province, and the Priority Academic Program Development of Jiangsu Higher Education Institutions.)

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Mast cells (MCs) are multifunctional immune cells that can maintain and regulate immune function. MCs originate in the bone marrow, arising in humans from CD34 +/CD117 + pluripotent progenitor cells (1). MCs circulate in the blood as committed precursors and then migrate to different organs and tissues, such as skin, lung and mucosal surfaces, where they undergo a final maturation and exhibit heterogeneity corresponding to the site. The phenotype of MCs is also influenced by the local microenvironment, especially blood vessels and nerve endings (2-4). MCs are also found in the brain, on the brain side of the blood-brain barrier (BBB), and in the leptomeninges. Almost 97% of MCs reside on the abluminal (brain) side of the blood vessels; thus, they are able to communicate with neurons, astrocytes, microglia, extracellular matrix, and blood vessels (5, 6).

MCs express many cell surface receptors, such as CD117 (c-kit receptors), which have the capacity to impact the responses of MCs

through the regulation of proliferation, migration, activation and enhancement of antigen-mediated MCs degranulation and cytokine production (7). The other major receptor responsible for regulating MCs function is their IgE receptor FcεR, which is activated by cross-linking and triggers the degranulation of MCs in many allergic and inflammatory diseases (8). Other receptors, such as FcgRIIa, TrkA, complement component receptors, Toll-like receptors (TLRs), and IL receptors, are involved in the activation of MCs (8-10).

The effective pathway of MC activation begins with the binding of IgE with its high-affinity receptor FcεR. Of course, other activation pathways are important in the absence of IgE in non-mammalian species (8). In allergic or non-allergic diseases, receptor agonists, intercellular contact and physical stimuli can cause the activation of MC degranulation, such as immunoglobulin light chain, complement, cytokines, temperature, and pressure (8). Upon activation, MCs release a number of mediators, including biogenic amines (histamine, 5 - serotonin), cytokines (IL-1, IL-6, tumour necrosis factor, interferon, growth factor), enzymes (trypsin, chymotrypsin, phospholipase), lipid metabolites (prostaglandins, leukotrienes, platelet activating factor), ATP, a neuropeptide (vasoactive intestinal peptide), growth factor, heparin, and nitric oxide (2). The degranulation of mast cells is divided into three steps. The first step is to release the presynthesized medium, including 5-serotonin, histamine, tryptase, heparin, and tumor necrosis factor. The second step is to rapidly synthesize lipid mediators. The third is the new synthesis of cytokines and chemokines (11, 12).

The activation and degranulation of MCs significantly modulate many aspects of physiological and pathological conditions in various settings. With respect to normal physiological functions, MCs regulate vasodilation, vascular homeostasis, innate and adaptive immune responses, angiogenesis, and venom detoxification (13, 14). In addition, MCs regulate functions of many cell types, such as dendritic cells, macrophages, T cells, B cells, fibroblasts, eosinophils, endothelial cells, and epithelial cells. MCs also play a significant role in the regulation of bone growth, remodeling, and mineral homeostasis (15). On the other hand, MCs have been implicated in the pathophysiology of many diseases, including anaphylaxis, asthma, gastrointestinal disorders, many types of malignancies, and cardiovascular diseases (15) (Figure 1). The severity of MC activation depends on a number of different factors, including genetic predisposition, the number and releasability of MCs involved in the reaction, the type of allergen, the presence of specific IgE, and the presence of certain comorbidities (16). Thus, MCs are indispensable innate immune cells in the body.

Mast Cells and IgE-Mediated Anaphylaxis

The triggering role of MCs in allergic reactions is well known. The MCs are widely distributed in areas with close contact with the external environment of the skin, gastrointestinal tract and respiratory tract. Soon after, contact with many different stimuli, MCs swiftly cause an allergic reaction (4). IgE-mediated mast cell activation is the most important pathway of degranulation of MCs. When the allergen first invades the body, the plasma cells secrete large amounts of antigen-specific immunoglobulin E (IgE). IgE binds to the mast cell-surface FcεRI via IgE's Fc region and causes the organism to be sensitized. When the allergen again invades the body, it will be specifically bound to two or more adjacent IgE antibodies on the surface of the sensitized MC surface, causing the membrane-surface FcεRI molecules to cross-link. This activates FcεRI, which activates Syk and Fyn protein tyrosine kinases by phosphorylation of the immunoreceptor tyrosine activation motifs (ITAMs) at their C-termini. These activated kinases form the initial signal of MC degranulation and cause MCs to rapidly degranulate, which means to release large amounts of inflammatory mediators, resulting in both rapid and delayed hypersensitivity reactions (17).

Histamine is a vasoactive substance that is released mainly by MCs. Histamine can cause itching, sneezing, and runny nose. In the body, vascular and tracheal smooth muscle and intestinal smooth muscle all express histamine receptor. When histamine is combined with its receptor, vasodilatation and increased permeability result, which leads to the transfer blood volume into the interstitial space, resulting in local edema

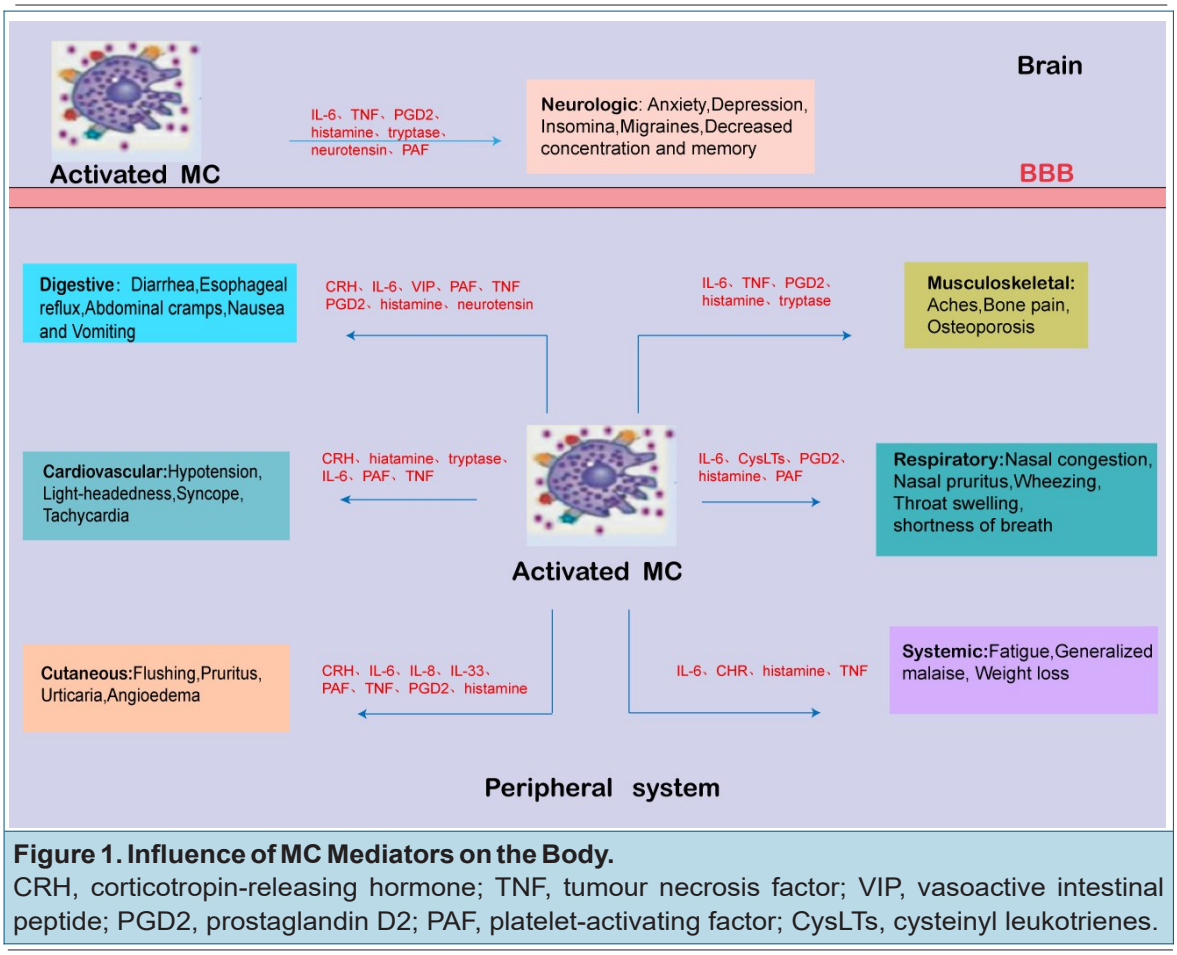

Figure 1. Influence of MC Mediators on the Body.
CRH, corticotropin-releasing hormone; TNF, tumour necrosis factor; VIP, vasoactive intestinal peptide; PGD2, prostaglandin D2; PAF, platelet-activating factor; CysLTs, cysteinyl leukotrienes.

and hypotension. Constriction of tracheal smooth muscle and mucous membrane edema result in tracheal stricture and breathing difficulty. Intestinal smooth muscle contractions and mucosal edema cause abdominal pain and diarrhea.

The four organ systems mainly involved with mast cell degranulation are skin (urticaria, angioedema, flush), the gastrointestinal tract (abdominal pain, nausea, diarrhea), the respiratory system (asthma, dyspnoea), and the cardiovascular system (hypotension, shock) (18, 19). Therefore, histamine and tryptase released from MCs are considered the basis for the diagnosis of anaphylaxis. Optimal blood sampling for measurement of histamine and tryptase should be performed 15–60 and 30–180 min after the onset of the symptoms, respectively. However, the results from these tests may not be specific for anaphylaxis (20).

Mast Cells and Inflammation Reactions

MCs are key structural and functional components of the immune system. These cells play a key role in inflammation progress (15, 21). MCs are activated to release various molecules contained in their cytoplasm, such as histamine, 5-serotonin (5-HT), tryptase, prostaglandins, cytokines, and chemokines. In addition, the pro-inflammatory cytokines secreted by MCs include, tumor necrosis factor-alpha (TNF-α), IL-1, IL-6 and IL-18 (2), which are important in inflammatory responses. In the inflammatory processes of hypoxia, ischemia-reperfusion and atherosclerosis, MCs released histamine, tryptase, chymase, pro-inflammatory cytokines, and other molecules into the interstitial medium, increasing the recruitment, adhesion, and invasion of neutrophils, as well as vascular permeability (15, 22).

There is increasing evidence that MCs are involved in the inflammatory processes of the central nervous system (CNS) (23, 24). Neuro-inflammation is a protective physiologic response by the organism aimed at removing detrimental stimuli and initiating tissue healing. When neuroinflammation is prolonged, it can surpass the bounds of physiological control and produce deleterious effects involving pro-inflammatory cytokine over-secretion, increased oxidative stress, BBB breakdown and death of nearby neurons (25). Under physiological conditions, the number of MCs in the brain is less than neurons, microglia and other brain cells. In the state of cerebral ischaemia, surgical stress and other pathological states, the number of mast cells in the brain increases rapidly, and they become activated, and act on the neurovascular unit (NVU) (vascular endothelial cells, pericytes, vascular smooth muscle cells, microglia and neurons) (5, 6). In the early stages of the pathogenesis of acute cerebral ischemia and cerebral hemorrhage, mast cells exhibit the rapid degranulation response in cerebral blood vessels and other parts of the CNS, releasing vasoactive and neuroactive synthetic medium in advance. The active medium acts on the basement membrane to disrupt the blood-brain barrier and; brain edema, promoting the infiltration of cells and hemorrhage (5). In addition, in acute cerebral ischemia injury, brain mast cells increase in number, which prolongs the expression of endothelial cell adhesion molecules, destroys the blood-brain barrier, and recruits neutrophils, macrophages, and other inflammatory cells into the center of the injury (26-28).

Converging sources of evidence point to a role for MC in the development of postoperation cognitive dysfunction (POCD) (20, 29, 30). The precise pathogenic mechanisms of POCD remain unclear. The most significant risk factor for POCD is advanced age, and surgical trauma is another risk factor. Peripheral surgery can induce neuroinflammatory responses, and pro-inflammatory cytokines, including TNF-α, IL-1β, IL-4 and IL-6, released into the periphery are capable of entering the brain, causing further neuroinflammatory responses and brain injury by activating microglia (31, 32). As mentioned above, MCs play an important role in central inflammation. Our study found that in vitro, activated MCs can induce microglia and astrocyte activation. In addition, activated MCs can directly induce neuronal apoptosis, which can be inhibited by the MCs stabilizer cromolyn. In vivo, site-directed pre-injection of cromolyn inhibits the surgery-induced MCs number increase in the hippocampus, astrocyte and microglia activation, and the production of inflammatory factors (TNF-α, IL-6). Meanwhile, site-directed pre-injection of cromolyn can improve the learning and memory abilities of animals (33, 34). Tibial fracture surgery decreases hippocampal occludin and claudin-5 protein levels and increases hippocampal MMP-2 and MMP-9, while the BBB permeability is elevated. However, those effects are inhibited by site-directed injection of cromolyn in the hippocampus (29). These results suggest that tibial fracture surgery can activate mast cells in the hippocampus, followed by microglia and astrocyte activation and BBB breakdown, causing damage to learning and memory in animals; cromolyn can stabilize mast cells, thereby inhibiting the activation of microglia and astrocytes, enhancing the stability of the blood-brain barrier, reducing inflammatory response and improving cognitive function.

Perioperative Management of Patients with Mast Cell Disease

MC diseases include mastocytosis and MC activation syndrome. Mastocytosis and MC activation syndrome are rare, and the actual incidences are unknown, but a recent study estimated that the incidence of mastocytosis was approximately 1/10000 (35). Because of the variety of clinical features and the presence of complications, it is difficult to diagnose. The diagnostic criteria currently include the clinical characteristics of MC mediators, the increase of MC media in serum, and the effectiveness of drugs targeting MCs and MC mediators (3, 16, 36). MC mediator-associated symptoms appear to be higher in mastocytosis patients than in the general population (9). During the perioperative period, various nonspecific stimuli can cause MC activation and degranulation, which further lead to allergic reactions and postoperative acute central inflam-

mation (30, 37). In the perioperative period, some opioids, such as codeine and morphine, and neuromuscular blocking drugs, such as atracurium and mivacurium, cause these reactions through MC activation and subsequent histamine release. In addition, the patient's mood, pain, stimulation, and type of surgery may promote MC activation and degranulation (38-40). MC degranulation is unpredictable, and any drug may cause MC activation. In the use of stupefacients, the lack of identifiable triggers is a major challenge for anesthesiologists, so that the main anesthetic concern is the avoidance of release of histamine and other MC mediators (37, 41). The perioperative management focuses on the following points:

1. An understanding of the disease and its clinical manifestations.

2. A careful preoperative history regarding the phenotype of the disease and its activity (e. g., forming blisters) and any previous immediate reactions.

3. Close communication between the anesthesiologist and surgeon before surgery.

4. The avoidance of known and possible factors triggering acute mediators release.

5. Management of perioperative MC degranulation and cardiovascular disturbances.

6. If a drug associated with MC activation should be discontinued during the operation and, in cases of unusual severe reactions, discontinue anesthetic agents likely to cause vasodilation and negative inotropic effects whenever possible.

7. In cases of cardiovascular disturbances (hypotension and eventual cardiovascular collapse), it is essential to dilate appropriately to compensate for peripheral vasodilation and capillary leakage resulting from the release of MC mediators.

8. When anaphylactic shock or even cardiac arrest occurs, epinephrine should be used as early as possible to constrict the blood vessels, stimulate the heart, and raise blood pressure, while establishing or ensuring the airway with 100% oxygen (31).

Prophylactic anti-mediator-therapy(PTA) given one hour before the operation and adequate anesthetic management appear to be effective in preventing / controlling MC mediator-associated symptoms (18).

Conclusions

MCs play a key role in regulating normal physiological processes and many pathological conditions. In recent years, research has shown that MCs are involved not only in allergy and asthma but also as the “first responders”, in focal cerebral ischemia, traumatic brain injury, multiple sclerosis, Alzheimer's disease and other inflammatory diseases. MCs can quickly degranulate to release various inflammatory mediators, activate glial cells and cause neuronal apoptosis (23). However, the role of MCs in central inflammatory diseases is not clear to date, and the role of MCs in neuritis is worthy of further study (29). Therefore, the anesthesiologist needs to understand these myriad roles of MCs to protect the patients' safety and improve postoperative rehabilitation.

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