Stress triggers coronary mast cells leading to cardiac events

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ABSTRACT

Objective: Stress precipitates and worsens not only asthma and atopic dermatitis but also acute coronary syndromes (ACSs), which are associated with coronary inflammation. Evidence linking stress to ACS was reviewed and indicated that activation of coronary mast cells (MCs) by stress, through corticotropin-releasing hormone (CRH) and other neuropeptides, contributes to coronary inflammation and coronary artery disease.

Data Sources: PubMed was searched (2005–2013) for articles using the following keywords: allergies, anaphylaxis, anxiety, coronary arteries, coronary artery disease, C-reactive protein, cytokines, chymase, histamine, hypersensitivity, interleukin-6 (IL-6), inflammation, mast cells, myocardial ischemia, niacin, platelet-activating factor, rupture, spasm, statins, stress, treatment, tryptase, and uroctortin.

Study Selections: Articles were selected based on their relevance to how stress affects ACS and how it activates coronary MCs, leading to coronary hypersensitivity, inflammation, and coronary artery disease.

Results: Stress can precipitate allergies and ACS. Stress stimulates MCs through the activation of high-affinity surface receptors for CRH, leading to a CRH-dependent increase in serum IL-6. Moreover, neurotensin secreted with CRH from peripheral nerves augments the effect of CRH and stimulates cardiac MCs to release IL-6, which is elevated in ACS and is an independent risk factor for myocardial ischemia. MCs also secrete CRH and uroctortin, which induces IL-6 release from cardiomyocytes. The presence of atherosclerosis increases the risk of cardiac MC activation owing to the stimulatory effect of lipoproteins and adipocytokines. Conditions such as Kounis syndrome, mastocytosis, and myalgic encephalopathy/chronic fatigue syndrome are particularly prone to coronary hypersensitivity reactions.

Conclusion: Inhibition of cardiac MCs may be a novel treatment approach.

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study of 8,838 healthy participants reported that “burnout” was an independent risk factor for future CAD over a 3.4-year period. A 10-year prospective Women’s Health Study reported a significant correlation between high-stress jobs, but not job insecurity, and CAD. Job strain also was associated with high blood levels of C-reactive protein (CRP). In another study, CAD-related events were higher in US firefighters during strenuous duties and more so in those with underlying CAD, resulting in CAD being the leading cause of death (45%).

In this report, the authors review the relevant literature and propose that activation of cardiact mast cells (MCs) by stress plays a key role in stress-induced CAD, especially because β-blockers do not prevent the effect of stress. Moreover, MCs have been implicated in obesity and obesity-related asthma, which are known a key role in stress-induced CAD, especially because β-blockers do not prevent the effect of stress. Moreover, MCs have been implicated in obesity and obesity-related asthma, which are known to cause elevation of plasma IL-6 in rats. Ucn also stimulates IL-6 secretion from human peripheral mononuclear cells in vitro and increases IL-6 mRNA levels through CRHR-2 activation in rat aortic smooth muscle cells. Moreover, Ucn can stimulate IL-6 release from neonatal cardiomyocytes. CRHR-2 might have proinflammatory actions through a mechanism that involves MCs. In contrast, Ucn has been generally considered cardioprotective, especially in ischemia–reperfusion injury, through upregulation of the p42–p44 mitogen-activated protein kinase pathway. Ucn-II and Ucn-III also are cardioprotective against ischemia–reperfusion injury. Stimulation of CRHR-2β by Ucn-II and Ucn-III decrease infarct size. However, the effects of CRH and related peptides may not always be the same and may depend on the stage of maturation of the target cells and/or activation of specific CRHR isomers, documented in keratinocytes and MCs. For instance, a soluble CRHR-2α isoform has been shown to neutralize the effect of CRH agonists. Moreover, in macrophages, CRHR-1 and CRHR-2 agonists have been shown to have an early stimulating effect, but a later inhibitory effect, on tumor necrosis factor-α (TNF-α) release.

**Regulation of the Stress Response**

Corticotropin-releasing hormone (CRH) activates the hypothalamic–pituitary–adrenal axis, typically leading to anti-inflammatory actions through the release of adrenal steroids. The effect of CRH is mediated through 2 main types of G-protein–coupled receptors, CRHR-1 and CRHR-2. The central nervous system and anterior pituitary express primarily CRHR-1, the activation of which leads to the release of adrenocorticotropic hormone. In addition to CRH, these receptors are activated by urotensin, sauvagine, and urocortins (Ucns) II and III, which are stronger agonists for CRHR-2. CRHR-2 has 3 different spliced forms (α, β, and γ), of which CRHR-2α is found mainly in the central nervous system and on MCs, whereas CRHR-2β, in addition to Ucn mRNA, is expressed predominantly in the heart and on cardiomyocytes, with CRHR-2β being predominantly expressed in the left ventricle.

Corticotropin-releasing hormone also can be released outside the central nervous system, where it has proinflammatory actions. Human skin expresses CRH and CRHR-1, which may act as a “peripheral hypothalamic–pituitary–adrenal axis” outside the brain. In addition to the hypothalamus, CRH is synthesized by skin cells, immune cells, and MCs. CRH secreted from MCs can decrease the ability of T-regulatory cells to produce the immunosuppressant interleukin (IL)-10, thus further increasing inflammation. This has led to the proposal that CRH may be involved in the pathophysiology of skin and other inflammatory diseases, especially when worsened by stress, through MC involvement.

Corticotropin-releasing hormone is often released together with another brain peptide, neurotensin (NT), which is vasoactive and has been implicated in inflammation. NT is increased in the skin after acute stress, stimulates skin MCs, and increases vascular permeability in rodents, an effect synergistic with CRH. NT stimulates rodent MCs to secrete histamine and elevates histamine plasma levels through the activation of NT receptors. Acute stress leads to increased skin vascular permeability, which is mimicked by the intradermal injection of CRH, an effect absent in MC-deficient mice. CRH also increases the microvasculature permeability of human skin in an MC-dependent manner. CRHR-1 gene is expressed on human cultured MCs, the activation of which induces the production of vascular endothelial growth factor. The authors recently reported that serum CRH was increased in patients with psoriasis and atopic dermatitis, as was NT in patients with psoriasis and atopic dermatitis.

Corticotropin-releasing hormone and Ucn secreted under acute stress have been implicated in the pathophysiology of neuro-inflammatory disorders and MI. Ucn mediates stress-induced IL-6 release in vivo, and administration of Ucn causes elevation of plasma IL-6 in rats. Ucn also stimulates IL-6 secretion from human peripheral mononuclear cells in vitro and increases IL-6 mRNA levels through CRHR-2 activation in rat aortic smooth muscle cells. Moreover, Ucn can stimulate IL-6 release from neonatal cardiomyocytes. CRHR-2 might have proinflammatory actions through a mechanism that involves MCs. In contrast, Ucn has been generally considered cardioprotective, especially in ischemia–reperfusion injury, through upregulation of the p42–p44 mitogen-activated protein kinase pathway. Ucn-II and Ucn-III also are cardioprotective against ischemia–reperfusion injury. Stimulation of CRHR-2β by Ucn-II and Ucn-III decrease infarct size. However, the effects of CRH and related peptides may not always be the same and may depend on the stage of maturation of the target cells and/or activation of specific CRHR isomers, documented in keratinocytes and MCs. For instance, a soluble CRHR-2α isoform has been shown to neutralize the effect of CRH agonists. Moreover, in macrophages, CRHR-1 and CRHR-2 agonists have been shown to have an early stimulating effect, but a later inhibitory effect, on tumor necrosis factor-α (TNF-α) release.

**Cardiovascular Mast Cells and CAD**

Mast cells are well known for their role in the pathogenesis of allergic reactions, but MCs are currently considered important in innate immunity and antigen presentation, and in inflammation. MCs originate from hemopoietic stem cells that differentiate in tissues under the influence of various tissue microenvironmental conditions, including nerve growth factor and mainly stem cell factor. MCs also are present in the heart, and cardiac MCs have been shown to differ from other connective tissue MCs in that they are not stimulated by morphine. MCs are present, especially in coronary arteries, during spasm, accumulate in the rupture-prone shoulder region of coronary atherosomas, and are associated specifically with plaque erosion and rupture. Degranulated MCs have been identified in the adventitia of vulnerable and ruptured lesions in patients with MI. MCs can be triggered by many molecules relevant to CAD, such as oxidized low-density lipoprotein (LDL) and complement fragment 5a, which has been implicated in ruptured coronary plaques in MI. Adventitial MCs are localized close to nerve endings in atherosclerotic coronary arteries and correlate with the number of nerve fibers. Nerve fibers immunoreactive for NT are also present in the heart, and NT can trigger coronary vasoconstriction.

Figure 1. Mast cells (black arrows) stained with toluidine blue close to a coronary blood vessel (white arrow) containing many erythrocytes from a mouse exposed to restraint stress for 30 minutes (magnification ×400).
Stress-induced cardiac MC degranulation has been found to be blocked by pretreatment with an NT-receptor antagonist. Reactive oxygen species also can activate MCs and release substance P (SP) from sensory nerves. The mitochondrial uncoupling protein-2, known to regulate reactive oxygen species production, has been reported to inhibit MC activation. SP treatment has been reported to significantly increase the number and extent of degranulation of adventitial MCs compared with controls and promote intraplaque hemorrhage; this was prevented by the neurokinin-1 receptor antagonist spantide I and was absent in MC-deficient ApoE-/- mice, which develop hyperlipidemia and spontaneous atherosclerosis. In addition to stimulating the secretion of histamine and other inflammatory mediators from human MCs, SP induces the release of vascular endothelial growth factor, an action augmented by IL-33. MC activation by SP or NT also results in mitochondrial translocation to the cell surface and extracellular release of mitochondrial, but not genomic, DNA, that acts as an “innate pathogen” inducing potent autocrine and paracrine inflammatory effects.

Mast cell–deficient LDLr-/- mice exhibited decreased atheroma size, lipid deposition, and T-cell and macrophage numbers compared with atherosclerosis-prone LDLr-/- mice. Adoptive transfer of bone marrow–derived MC precursors from normal wild-type mice to LDLr-/- kitw-sh/w-sh mice restored atherogenesis; however, when IL-6- and interferon-γ–deficient MCs were reconstituted, the atherogenesis failed to occur. MC-deficient kitw-sh/w-sh mice have significantly lower serum cholesterol and triglyceride levels with a concomitant decrease in atherogenic apolipoprotein-B–containing particles.

Therefore, cardiac MCs might participate in the development of atherosclerosis, coronary inflammation, and cardiac ischemia (Fig 2), in addition to their activation with stress.

**Mast Cell Mediators and CAD**

Many MC-derived mediators have profound effects on the cardiovascular system (Table 1). The proinflammatory cytokine IL-6 is thought to contribute to the development of CAD, ACS, and MI. Increased serum levels of CRP and IL-6, especially intracardiac IL-6, are considered independent risk factors for CAD. High plaque levels of CRP and IL-6 have been significantly correlated to increased risk of CAD.

The Health ABC study showed that plasma IL-6 levels had a stronger association with CRP than with CAD, whereas the PRIME study (étude PRospective du l’Infarctus MyocardE; prospective epidemiological study of myocardial infarction) showed that only IL-6 remained significantly associated with MI. The incidence of future acute coronary events and mortality of patients with stable CAD or healed MI also was strongly correlated with serum IL-6 levels over a 6-year observation period. Acute restraint stress increased plasma levels of IL-6 uniquely in an MC-dependent manner. Serum IL-6 also was increased in ischemia–reperfusion in mice and the levels correlated with the extent of cardiac tissue necrosis, but were absent in

**Stress**

**CRH/urocortin**

**Neurotensin**

**Adenosine**

**Thrombin**

**Endothelin**

**Histamine**

**Renin**

**Chymase and Tryptase**

**Angiotensin II**

**Inflammation +MMP’s activation**

**Inflammation**

**Leukocyte chemotaxis**

**Inflammation +MMP’s activation**

**Platelet activation**

**Destabilization of atherosclerotic plaque and thrombosis**

**Acute Coronary Syndromes**

**Coronary Vasospasm**

**Figure 2.** Diagrammatic representation of possible triggers of cardiovascular mast cells and their key mediators with coronary artery disease–relevant actions and major pathologic sequelae. CRH, corticotropin-releasing hormone; IL, interleukin; MMP, matrix metalloproteinase; PAF, platelet-activating factor; ROS, reactive oxygen species; TNF, tumor necrosis factor.

**Table 1**

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Cardiovascular effect</th>
</tr>
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<tbody>
<tr>
<td>Chymase</td>
<td>Generates angiotensin II, vasoconstriction, MMP-1 activation, endothelial cell apoptosis, formation of foam cells</td>
</tr>
<tr>
<td>CRH</td>
<td>Autocrine MC and immune cell stimulation</td>
</tr>
<tr>
<td>Histamine</td>
<td>Coronary artery constriction, stimulation of endothelial cell IL-6 and IL-8 release, P-selectin upregulation, potentiation of the effect of PAF, induction of microvascular permeability, deposition of LDL in intima</td>
</tr>
<tr>
<td>IL-6</td>
<td>Proinflammatory, CRP induction, T-helper cell type 17 maturation, leukocyte recruitment</td>
</tr>
<tr>
<td>IL-8</td>
<td>Immune cell chemotaxis</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>Coronary vasoconstriction</td>
</tr>
<tr>
<td>MMP-9</td>
<td>Matrix and vascular integrity degradation</td>
</tr>
<tr>
<td>PAF</td>
<td>Platelet activation and aggregation, proinflammatory</td>
</tr>
<tr>
<td>Neurotensin</td>
<td>Proinflammatory, vasocostriction</td>
</tr>
<tr>
<td>Thromboxanes</td>
<td>Platelet aggregation, vasoconstriction</td>
</tr>
<tr>
<td>Renin</td>
<td>Angiotensin I synthesis, vasoconstriction</td>
</tr>
<tr>
<td>TNF</td>
<td>Proinflammatory, IL-6 upregulation, MMP activation, endothelial cell apoptosis</td>
</tr>
<tr>
<td>Tryptase</td>
<td>Proinflammatory, PAR-2 activation, HDL degradation, endothelial apoptosis, induction of microvascular permeability, deposition of LDL in intima</td>
</tr>
<tr>
<td>Urocortin</td>
<td>Cardiomyocyte IL-6 release</td>
</tr>
</tbody>
</table>

Abbreviations: CRH, corticotropin-releasing hormone; CRP, C-reactive protein; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; MC, mast cell; MMP, matrix metalloproteinase; PAF, platelet-activating factor; PAR, protease-activated receptor; T helper cell type 17; TNF, tumor necrosis factor.
MC-deficient mice. Cardiomyocytes released IL-6 in response to hyposensitive stress and to cytokines. Moreover, IL-1 expressed from the secondary inflammatory plaque stimulated MCs to release IL-6 selectively without degranulation. MC-derived IL-1 was shown to drive skin inflammation; this IL-1 also induced vascular leakage and recruited neutrophils in histamine-dependent urticaria.

Human coronary artery specimens contain MCs that also store and release TNF. MCs can secrete preformed TNF and release newly synthesized TNF in response to lipopolysaccharide. In fact, MCs are the only immune cells that store preformed TNF in their secretory granules and can secrete it rapidly. Obviously, endothelial cells and other immune cells participate. MC-derived TNF contributes to the upregulation of IL-6 in infiltrating leukocytes and initiates the cytokine cascade responsible for myocyte intercellular adhesion molecule-1 induction and subsequent neutrophil-induced injury. The fact that TNF is degraded quickly supports the importance of local TNF secretion. Cardiac MCs also secrete renin during ischemia—reperfusion, thus initiating local angiotensin formation.

Moreover, chymase is the main cardiac source of converting enzyme-generating angiotensin II, which has potent vasoconstrictor and pro-arrhythmogenic actions. MC chymase also activates pro-matrix metalloproteinase-1, and human MCs also secrete matrix metalloproteinase-9 and can enhance T-cell activation on contact with activated T cells and through TNF. Chymase, tryptase, and cathepsin G can degrade vascular endothelial cadherin, a molecule involved in the survival signaling of endothelial cells. Although 1 study reported that there was no correlation between serum chymase level and CAD, it is the local release of chymase and other mediators that would be important. Tryptase further leads to inflammation through protease-activated receptors that also are present on MCs and can be stimulated by thrombin.

Persistent serum tryptase elevations have been detected in patients with acute ACS and stable CAD. Higher serum tryptase and chymase levels have been found in nonallergic patients with acute MI and unstable angina compared with patients without substantial CAD. Elevated tryptase also has been noted in coronary syndrome and hypersensitivity reactions.

Increased histamine levels have been observed in the great cardiac vein in patients with attacks of variant angina unrelated to an allergic event. Histamine is a coronary vasoconstrictor, and 1 study found that blood concentrations were more than twice that compared with control normal subjects. Histamine induces endothelial cell release of IL-6 and IL-8, the production of which is enhanced by lipopolysaccharide and TNF-α, which can contribute to endothelial apoptosis.

Mast cell–derived leukotrienes exhibit strong proinflammatory activities in cardiovascular tissues. Leukotrienes also are powerful vasoconstrictors and their biosynthesis is enhanced in the acute phase of unstable angina. Expression of the 5-lipoxygenase pathway is increased in arterial walls of patients with various stages of atherosclerosis, and MCs in atherosclerotic plaques express 5-lipoxygenase. Deficiency of 1 5-lipoxygenase allele was found to be potent protection against atherosclerosis development in LDLr-/- mice, and leukotriene B4 receptor antagonism also was protective in several atherosclerosis-susceptible mouse strains.

Platelet-activating factor (PAF) is another molecule generated from arachidonic acid, much like the leukotrienes, but from the conversion of ether-linked phospholipids. PAF has been implicated in allergic inflammation, especially asthma and anaphylaxis. PAF can be released from MCs and stimulates MCs. PAF has been implicated in the pathogenesis of CAD. In particular, elevated PAF acetylhydrolase levels have been reported in ACS, MC activation syndrome, which presents with signs and symptoms of mastocytosis without elevated serum or urine markers, has been associated with cerebral vasospasm, a Kounis-like syndrome.

Coronary Hypersensitivity Syndromes

There is evidence pointing to a possible association between allergy and the cardiovascular system and between asthma and CAD. Moreover, air pollution has been associated with an increased incidence of deaths from CAD. Patients with elevated serum tryptase are diagnosed with mastocytosis, a rare disease characterized by a large number of hyper-responsive MCs and cardiovascular problems.

Acute coronary syndrome, coronary spasm, acute MI, and stent thrombosis in the setting of allergic or anaphylactic reactions has been termed Kounis syndrome. This syndrome is increasingly recognized in different clinical settings and has been associated with gelofusine, latex exposure, ceftriaxone, eosinophilic periarthritis, and coronary stents. Whether MCs are activated at contact with metal or drug-coated stents remains to be investigated.

Cardiovascular symptoms also are present in many patients with myalgic encephalopathy/chronic fatigue syndrome, characterized by debilitating fatigue for longer than 3 months and neurohormonal and sleep disturbances. Such patients show high heart rate and peripheral resistance on the 20° “tilt-table” test compared with controls. Myalgic encephalopathy/chronic fatigue syndrome symptoms worsen with stress and may be associated with brain MC activation.

Given these findings, it is apparent that inhibiting MC activation would be beneficial in coronary hypersensitivity syndromes and in CAD, although coronary MCs may be one of the many cell types involved. The ability of MCs to secrete many mediators selectively allows MCs to participate in different types of reactions and serve as immunomodulatory cells. Clearly, such actions need not be addressed in the acute setting.

Clinical Implications

Treatment of the allergic event with intravenous hydrocortisone and histamine receptor-1,2 antagonists usually also decreases cardiovascular symptoms. Subcutaneous allergen-specific immunotherapy used for the treatment of IgE-mediated allergic diseases has been associated with a lower risk of acute MI and autoimmune disease. Endothelin-1 is increased in patients with atherosclerosis and coronary endothelial dysfunction. Administration of endothelin-1 to blood-perfused, isolated rat hearts has resulted in extensive MC degranulation and increased matrix metalloproteinase-2 activity.

Long-term administration of endothelin-1 receptor antagonists has improved coronary endothelial function in patients with early atherosclerosis.

For those patients with documented CAD, statins have been helpful in decreasing atherosclerosis. Statins also have been shown to have anti-inflammatory effects and lowers total cholesterol and LDL, increases high-density lipoprotein, and prevents the release of inflammatory mediators from adipocytes. However, compliance with niacin is severely limited by “flush,” characterized by erythema, itching, and a sense of warmth and discomfort, that occurs even in slow- or extended-release forms. Nevertheless, use of statins and niacin to address underlying atherosclerosis is likely to decrease the risk of coronary hypersensitivity, especially from stress.

Unfortunately, there is no effective human MC inhibitor clinically available. Disodium cromoglycate (cromolyn) inhibits histamine secretion from rat peritoneal, but not intestinal, MCs.
Cromolyn has been reported to improve only gastrointestinal symptoms in patients with mastocytosis; yet, it did not inhibit human gastrointestinal or lung mucosal MCs. More recently, cromolyn has been reported to not inhibit even mouse MCs. Cromolyn is a weak inhibitor of cultured human MCs and is particularly useful in allergic rhinitis and urticaria. Cromolyn can inhibit mediator release from human MCs and can block the ability of PAF to stimulate human MCs through an action unrelated to its histamine-1 receptor blocking properties. Interleukin-10 is produced mostly by T Helper type 2 cells, macrophages, and CD8+CD4+ cell clones. It can inhibit the synthesis and release of several proinflammatory cytokines in antigen- or mitogen-activated rodent MCs. IL-10 also inhibits IL-6 and TNF, but not preformed mediator release, from rat peritoneal MCs. Moreover, IL-10 gene transfer apparently protects against acute mustard oils in rats and downregulates the expression of the IgE receptor in mouse MCs. However, the effect of IL-10 on human MCs is not clear because IL-10 does not inhibit tryptase and IL-6 from human leukemic MCs.

The naturally occurring flavonoids, luteolin and quercetin, have potent antioxidant and anti-inflammatory activities and are generally considered safe. Flavonols have been proposed as a polyphenolic drink could lower urinary biomarkers of CAD. A double-blinded, placebo agents and decreasing atherosclerosis and stress may be novel approaches to treat patients with mastocytosis, but apparently through an action on sensory nerve endings, rather than on skin MCs.

Some histamine-1 receptor antagonists have MC blocking actions and could be used prophylactically. Rupatadine is a histamine-1 receptor antagonist, which also inhibits the actions of PAF and TNF, but not preformed mediator release, from rat peritoneal MCs. Moreover, IL-10 gene transfer apparently protects against acute mustard oils in rats and downregulates the expression of the IgE receptor in mouse MCs. However, the effect of IL-10 on human MCs is not clear because IL-10 does not inhibit tryptase and IL-6 from human leukemic MCs.

The flavonol quercetin has been shown to inhibit rat mucosal MCs when cromolyn was ineffective. Quercetin also inhibits MCs when cromolyn was ineffective. Quercetin also inhibits mediator release of several proinflammatory cytokines,176 including IL-6. The flavone luteolin also inhibits human MCs,173 suppresses adipocyte activation of macrophages, inhibits inflammation,174 increases insulin sensitivity of the endothelium,175 and inhibits MC-dependent T-cell stimulation.176 Moreover, luteolin prevents niacin-induced flush.178

Stress reduction through transcendental meditation in a randomized control trial has been found to significantly decrease the risk of mortality from MI and stroke in patients with CAD. The Responses of Mental Stress–Induced Myocardial Ischemia to Escitalopram Treatment (REMIT) trial concluded that administration of escitalopram (5 mg/d, titrated up to 20 mg/d) for 6 weeks resulted in a lower rate of mental stress–induced, but not exercise-induced, MI compared with controls.

Conclusion

Increasing evidence indicates that stress worsens or precipitates CAD through the stimulation of coronary MCs, leading to inflammation. This effect may be more pronounced in patients with atherosclerosis or during acute MI activation by allergic or nonallergic triggers. Combining anti-inflammatory and MC inhibitory agents and decreasing atherosclerosis and stress may be novel treatment approaches. Certain natural flavonoids may be particularly useful in this respect and should be tested in controlled clinical trials.

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