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Stress triggers coronary mast cells leading to cardiac events

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Keywords

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Introduction

There is considerable evidence that stress worsens allergies[1-4], asthma[5, 6], as well as skin diseases[7]. Prenatal stress has been associated with increased cord blood imunnoglobulin (IgE), and this correlation was stronger between mothers with a history of atopy and offspring sensitive to dust mites[8]. Acute stress is also implicated in cardiovascular pathology[1], especially in eliciting myocardial ischemia (MI) in patients with coronary artery disease (CAD)[9]. MI occurring without angina on presentation appears to make up a sizable portion of the MI population[10-12]. Recent papers have confirmed that psychological and social stressors contribute to CAD[13]. However, the mechanism of this effect is not well understood.

In a prospective cohort study (Whitehall II) of 7,268 subjects, the perception that stress worsens health was significantly associated with increased CAD risk[14]. Results from the

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same study indicated that job insecurity was associated with higher incidence of CAD-associated events[15]. Moreover, mental-stress-induced ischemia was more common than exercise-induced ischemia in patients with clinically stable CAD[16]. A cohort study of 4,204 patients with acute MI showed that perceived stress was associated with adverse one year health outcomes[17]. An independent Meta analysis of 6 studies with 118,696 total subjects reported a significant association between high perceived stress and increased risk of CAD[18].

A Meta analysis of 13 European studies (1985-2003) concluded that job strain increased the risk for CAD[19]. Another prospective study of 8,838 healthy participants, reported that "burnout" was as independent risk factor for future CAD over a 3.4 year period[20]. A ten year prospective Women's Health study reported a significant correlation between high strain jobs, but not job insecurity, and CAD[21]. Job strain was also associated with high blood C-reactive protein (CRP)[22]. CAD-related events were higher in US firefighters during strenuous duties and more so in those subjects with underlying CAD resulting in CAD being the leading cause of death (45%)[23].

Here we review the relevant literature and propose that activation of cardiac mast cells (MC) by stress plays a key role in stress-induced CAD, especially since beta-blockers do not prevent the effect of stress. Moreover, MC have also been implicated in obesity [24] and obesity-related asthma[25], which are known risk factors for CAD[26]. ACS clinically manifest themselves as unstable angina or acute MI and are most commonly caused by the rupture of atherosclerotic plaques. However, a key component of CAD is local inflammation [27, 28] not only of the intima, but also of the arterial adventitia that may be more important than simple cholesterol accumulation because the inflammatory plaque is more likely to break off and cause MI[29].

Regulation of the stress response

CRH activates the hypothalamic-pituitary-adrenal (HPA) axis typically leading to anti-inflammatory actions through release of adrenal steroids. The effect of CRH is mediated through two main types of G protein-coupled receptors, CRHR-1 and CRHR-2. The CNS and the anterior pituitary express primarily CRHR-1, activation of which leads to release of adrenocorticotropic hormone. In addition to CRH, these receptors are activated by urotensin, sauvagine and the urocortins (Ucn), Ucn-II and Ucn-III, which are stronger agonists for CRHR-2[30]. CRHR-2 has three different spliced forms (α, β and γ) of which CRHR-2α is found mainly in the CNS and on MC[31], while CRHR-2β, along with Ucn mRNA, is predominantly expressed in the heart and on cardiomyocytes, with CRHR-2β being predominantly expressed in the left ventricle[32].

CRH can also be released outside the central nervous system (CNS) where it has pro-inflammatory actions[33]. Human skin expresses CRH and CRHR-1 that may act as a "peripheral HPA axis" outside the brain[30]. In addition to the hypothalamus, CRH is synthesized by skin cells immune cells, and MC[34]. CRH secreted from MC can decrease the ability of T-regulatory (Treg) cells to produce the immunosuppressant interleukin-10 (IL-10), thus further increasing inflammation[35]. This has led to the proposal that CRH may

be involved in the pathophysiology of skin and other inflammatory diseases[36, 37], especially when worsened by stress, through MC involvement[33].

CRH is often released together with another brain peptide, neurotensin (NT), which is vasoactive and has also been implicated in inflammation[38]. NT is increased in the skin following acute stress, stimulates skin MC and increases vascular permeability in rodents, an effect synergistic with CRH[39]. NT stimulates rodent MC to secrete histamine and elevates histamine plasma levels through activation of NT receptors (NTR) [40].

Acute stress leads to increased skin vascular permeability, mimicked by intradermal injection of CRH, effects absent in MC deficient mice[41]. CRH also increases microvasculature permeability of human skin in an MC-dependent manner[42]. CRHR-1 gene is expressed on human cultured MC, activation of which induces production of vascular endothelial growth factor (VEGF)[31] . We recently reported that serum CRH was increased in psoriasis (Ps) and atopic dermatitis (AD)[43] patients, and so was NT in Ps [43] and AD patients[44].

CRH and Ucn secreted under acute stress, have been implicated in the pathophysiology of neuroinflammatory disorders[45] and MI[9, 46]. 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*, as well as increase IL-6 mRNA levels through CRHR-2 activation in rat aortic smooth muscle cells[47]. Moreover, Ucn can stimulate IL-6 release from neonatal cardiomyocytes[48]. CRHR-2 could have pro-inflammatory actions [45] through a mechanism that involves MC [33]. On the other hand, Ucn has been generally considered to be cardioprotective, especially in ischemia-reperfusion (IR) injury[49], through upregulation of the p42/p44 MAPK pathway[50]. Ucn-II and Ucn-III are also cardioprotective against IR injury[51, 52]. Stimulation of CRHR-2β by Ucn-II and III reduced infarct size[51]. 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 isoforms, documented in keratinocytes and MC[31]. For instance, a soluble CRHR-2α isoform was shown to neutralize the effect of CRH agonists[53]. Moreover, in macrophages, CRHR-1 and CRHR-2 agonists have an early stimulating effect, but a later inhibitory effect, on TNF-α release[54].

Cardiovascular mast cells and CAD

MC are well-known for their role in the pathogenesis of allergic reactions[55], but MC are now considered important in innate [56] and acquired immunity[57], antigen presentation[58], and inflammation[59]. MC originate from haemopoietic stem cells that differentiate in tissues under the influence of various tissue microenvironmental conditions, including nerve growth factor (NGF) and mainly stem cell factor (SCF)[60] . MC are also present in the heart[61], and cardiac MC were shown to differ from other connective tissue MC in that they were not stimulated by morphine[62]. MC are present especially in coronary arteries during spasm, they accumulate in the rupture prone shoulder region of the coronary atheromas[63] (Fig. 1), and are associated specifically with plaque erosion and rupture[64]. Degranulated MC were also identified in the adventitia of vulnerable and ruptured lesions in patients with MI[64]. MC can be triggered by many molecules relevant to CAD such as oxidized low density lipoprotein

(LDL)[65], and complement fragment 5a (C5a), which is implicated in ruptured coronary plaques in MI[66]. Adventitial MC are localized close to nerve endings in atherosclerotic coronary arteries and correlated with the number of nerve fibers[67]. Nerve fibers immunoreactive for NT are also present in the heart, and NT can trigger coronary vasoconstriction[68]. Stress-induced cardiac MC degranulation was blocked by preatreatment with a NT-receptor antagonist[69]. Reactive oxygen species (ROS) can also activate MC[70] and release substance P (SP) from sensory nerves. The mitochondrial Uncoupling Protein 2 (UCP2), known to regulate ROS production, was reported to inhibit mast cell activation[71]. SP treatment significantly enhanced the number and extent of degranulation of adventitial MC compared to controls, and promoted intraplaque hemorrhage; this was prevented by the neurokinin-1 receptor antagonist Spantide I and was absent in MC deficient ApoE$^{-/-}$ mice[67], which develop hyperlipidemia and spontaneous atherosclerosis. In addition to stimulating the secretion of histamine and other inflammatory mediators from human MC, SP also induced release of VEGF, an action augmented by IL-33[72]. MC activation by SP or NT also results in mitochondrial translocation to the cell surface[73], and extracellular release of mitochondrial, but not genomic, DNA, that acts as an “innate pathogen” inducing potent autocrine and paracrine inflammatory effects[74] .

Mast cell deficient LDLr$^{-/-}$ mice had decreased atheroma size, lipid deposition, as well as T-cell and macrophage numbers as compared to atherosclerosis-prone LDLr$^{-/-}$ mice[75]. Adoptive transfer of bone marrrow-derived MC precursors from normal wild type mice to LDLr$^{-/-}$ kit$^{w\text{-}sh/w\text{-}sh}$ mice restored atherogenesis; however when IL-6 and interferon-γ (IFN-γ) deficient MC were reconstituted, the atherogenesis failed to occur[75]. MC-deficient kit$^{w\text{-}sh/w\text{-}sh}$ mice had significantly lower serum cholesterol and triglyceride levels with a concomitant decrease in atherogenic apoB-containing particles[76].

Cardiac MC could, therefore, participate in the development of atherosclerosis, coronary inflammation and cardiac ischemia (Table 1), in addition to their activation with stress.

Mast cell mediators and CAD

Many MC-derived mediators have profounf effects on the cardiovascular system (Table 1). The pro-inflammatory cytokine IL-6 is thought to contribute to the development of CAD, ACS[77] and MI[78]. Increased serum levels of CRP[79] and IL-6[79], especially intracardiac IL-6 [77] are considered independent risk factors for CAD. High plaque levels of CRP and IL-6 were significantly correlated to increased risk of CAD[80]. The Health ABC study showed that plasma IL-6 levels had a stronger association with CRP than CAD, while the PRIME study 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 was also strongly correlated with serum IL-6 levels over a 6 year observation period[81]. Acute restraint stress increased plasma levels of IL-6 uniquely in a mast cell-dependent manner[82]. Serum IL-6 was also increased in I/R in mice and the levels correlated with the extent of cardiac tissue necrosis, but were again absent in mast cell deficient mice[83]. Cardiomyocytes released IL-6 in response to hypoxic stress and to cytokines. Moreover, IL-1 expressed from the secondary inflammatory plaque could stimulate MC to release IL-6 [84] selectively without degranulation[85]. MC-derived IL-1 was shown to drive

skin inflammation[86]; this IL-1 also induced vascular leakage and recruited neutrophils in histamine-dependent urticaria[87].

Human coronary artery specimens contain MC that also store and release TNF [88]. MC can secrete preformed TNF, while they also release newly synthesized TNF in response to LPS[73]. In fact, MC are the only immune cells that store preformed TNF in their secretory granules and can secrete it rapidly[89]. 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 (ICAM-1) induction and subsequent neutrophil-induced injury. The fact that TNF is degraded quickly supports the importance of the local TNF secretion. Cardiac MC also secrete renin during IR, thus initiating local angiotensin formation[90]. Moreover, chymase is the main cardiac source of converting enzyme generating angiotensin II, which has potent vasoconstrictor and pro-arrhythmogenic actions[90]. MC chymase also activates pro-matrix metaloproteinase-1 (MMP-1), and human MC also secrete MMP-9 and can enhance T cell activation[91] on contact with activated T-cells and through TNF[92]. Chymase, tryptase, and cathepsin G can degrade vascular endothelial cadherin, a molecule involved in the survival signaling of endothelial cells[93]. Even though one study reported that there was no correlation between serum chymase level and CAD[94], it is local release of chymase and other mediators that would be important. Tryptase further leads to inflammation through protease activated receptors (PARs), that are also present on MC and can be stimulated by thrombin.[95]. Persistent serum tryptase elevations were detected in patients with both acute ACS and stable CAD[96]. Serum tryptase and chymase were higher in nonallergic patients with acute MI and unstable angina than in patients without substantial CAD[97]. Elevated tryptase was also noted in coronary syndrome and hypersensitivity reactions[97].

Histamine levels were increased in the great cardiac vein in patients suffering from attacks of variant angina unrelated to an allergic event [98]. Histamine is a coronary vasoconstrictor and blood concentrations were more than twice that of age- and sex-matched controls in patients with ACS in the absence of any allergies[99]. Histamine blood levels were also significantly higher in patients with unstable angina and acute MI when compared with control normal subjects[100]. Histamine induces endothelial cell release of IL-6 and IL-8, production of which is enhanced by LPS and TNF-α, which can also contribute to endothelial apoptosis[101].

MC-derived leukotrienes exhibit strong pro-inflammatory activities in cardiovascular tissues. Leukotrienes are also powerful vasoconstrictors and their biosynthesis is enhanced in the acute phase of unstable angina[102]. Expression of the 5-lipoxygenase (5-LO) pathway is increased in arterial walls of patients with various stages of atherosclerosis, and MC in atherosclerotic plaques express 5-LO[103]. Deficiency of one 5-LO allele potent protection against atherosclerosis development of LDLr $^{-/-}$ mice, and leukotriene B_4 receptor antagonism was also protective in several atherosclerosis susceptible mouse strains[103].

Platelet Activating Factor (PAF) is another molecule generated from arachidonic acid, much like the leukotrienes, but from the conversion of ether-linked phospholipids[104]. PAF has been implicated in allergic inflammation, especially asthma[105, 106] and anaphylaxis[107]. PAF

can be released from mast cells[108] and also stimulates mast cells[109]. PAF has been implicated in the pathogenesis of CAD[110-112] In particular, elevated PAF acetylhydrolase levels have been reported in ACS[113-118]. Mast cell activation syndrome (MCAS), which presents with signs and symptoms of mastocytosis without elevated serum or urine markers[119], has been associated with cerebral vasospasm- a Kounis- like syndrome[120].

Coronary hypersensitivity syndromes

There is evidence pointing to a possible association between allergy and the cardiovascular system[121, 122], as well as between asthma and CAD[123]. Moreover, air pollution was found to be associated with increased incidence of deaths from CAD[124]. Patients with elevated serum tryptase are diagnosed with mastocytosis, a rare disease characterized by high number of hyperresponsive MC and cardiovascular problems[119, 125, 126].

ACS, coronary spasm, acute MI and stent thrombosis in the setting of allergic or anaphylactic reactions has been termed Kounis syndrome [127-129]. This syndrome is increasingly recognized in different clinical settings and has been associated with gelofusin[130], Latex exposure[131] ceftriaxone[132] eosinophilic periarteritis [133] and coronary stents[132, 134-136]. Whether MC are activated upong contact with metal or drug-coated stents remaines to be investigated.

Cardiovascular symptoms are also present in many patients with ME/CFS[137, 138], characterized by debilitating fatigue for over 3 months, as well as neurohormonal and sleep disturbances. Such patients show high heart rate and peripheral resistance on 20 degree “tilt-table” test as compared to controls[139]. ME/CFS symptoms worsen with stress and may be associated with brain MC activation[140].

Given the above, it is apparent that inhibiting MC activation would be beneficial in coronary hypersensitivity syndromes, but also in CAD even though coronary MC may be one of the many cell types involved. The ability of MC to secrete a number of mediators selectively[85], allows MC to participate in different types of reactions[59], as well as serve as immunomodulatory cells[141-144]. 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 reduces cardiovascular symptoms. Subcutaneous allergen-specific immunotherapy used for treatment of IgE-mediated allergic diseases was associated with lower risk of acute MI and autoimmune disease[145]. Endothelin-1 (ET-1) is increased in patients with atherosclerosis and coronary endothelial dysfunction. Administration of ET-1 to blood-perfused, isolated rat hearts resulted in extensive MC degranulation and increased MMP-2 activity[146]. Long term administration of ET-1 receptor antagonists improves coronary endothelial function in patients with early atherosclerosis[147].

For those patients with documented CAD, statins have been helpful in reducing atherosclerosis[148]. Statins have also been shown to have anti-inflammatory effects[27, 109, 148, 149]. Niacin reduces total cholesterol and LDL, while increasing HDL[150],

and also prevents release of inflammatory mediators from adipocytes[150]. However, compliance with niacin is severely limited by “flush”, characterized by erythema, itching and a sense of warmth and discomorft, that occurs even in slow or extended release forms[151]. Nevertheless, use of statins and niacin to address underlying atherosclerosis is likely to also reduce the risk of coronary hypersensitivity, especially due to stress.

Unfortunately, there is no effective human MC inhibitor clinically available. Disodium cromoglycate (cromolyn) inhibits histamine secretion from rat peritoneal[152], but not intestinal [153, 154] MC. Cromolyn was reported to improve *only* gastrointestinal symptoms in patients with mastocytosis[155], even though it could not inhibit human gastrointestinal or lung mucosal MC[156]. More recently, cromolyn was reported to not even inhibit mouse MC[157, 158]. Cromolyn is a weak inhibitor of contact dermatitis and phtosensitivity in humans[157, 158]. In fact, it was recently shown that a cromolyn cream was able to reduce itching in patients with mastocytosis, but apparently through an action on sensory nerve endings, rather than on skin MC[159].

Some H1-receptor antagonists have MC blocking actions and could be used prophylactically. Rupatadine is a histamine-1 (H1) -receptor antagonist, which also inhibits the actions of PAF[160,161] and is particularly useful in allergic rhinitis and urticaria[161, 162]. Rupatadine can inhibit mediator release from human MC[163] and can also block the ability of PAF to stimulate human MC through an action unrelated to its H1-receptor blocking properties[164].

IL-10 is produced mostly by Th2 cells, macrophages and $CD8^+$ cell clones. It can inhibit the synthesis and release of several pro-inflammatory cytokines in antigen or mitogen-activated rodent MC[165]. IL -10 also inhibits IL-6 [166] and TNF[167], but not preformed mediator release from rat peritoneal MC[166]. Moreover, IL-10 gene transfer apparently protects against acute myocarditis in rats[168], and downregulates the expression of the IgE receptor in mouse MC[169]. However, the effect of IL-10 on *human* MC mast cells is not clear because IL-10 does not inhibit tryptase and IL-6 from human leukemic mast cells[170].

The naturally occurring flavonoids, luteolin and quercetin, have potent anti-oxidant and anti-inflammatory actions [171-173], and are generally considered safe[174, 175]. Flavonols have been proposed as possible therapeutic agents for CAD [176-178]. Meta analysis of epidemiological studies shows an inverse relationship between flavonol/flavone intake and CAD[179]. A review of twenty publications from twelve prospective cohorts in European and US populations reported that consumption of flavonoids and flavones were most strongly associated with lower CAD mortality[180]. A double-blind, placebo-controlled, randomized clinical study using the polyhenolic compound Pycnogenol showed improved endothelial function in patients with CAD[109]. A pilot study of 2 week consumption of a polyphenolic drink lowered urinary biomarkers of CAD[181].

The flavonol quercetin was shown to inhibit rat mucosal mast cells, when quercetin was ieffective[156, 182]. Quercetin also inhibits human mast cell release of pro-inflammatory cytokines[176], including IL-6[84]. The flavone luteolin also inhibits human MC[183], suppresses adipocyte activation of macrophages, inhibits inflammation [184, 185], increases insulin

sensitivity of the endothelium[184], and inhibits MC-dependent T cell stimulation[91]. Moreover, luteolin prevented niacin-induced flush [186, 187].

Stress reduction through transcedental medication in a randomized control trial significantly reduced risk of mortality MI and stroke in patients with CAD[188]. The Responses of Mental Stress-Induced Myocardial Ischemia to Escitalopram Ttreatment (REMIT) trial concluded that administration of escitalopram (5 mg/day titrated up to 20 mg/day) for 6 weeks resulted in lower rate of mental stress-induced, but not exercise-induced, MI compared to controls[189].

Concluding remarks

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

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Abbreviations

ACS	acute coronary syndrome
CAD	coronary artery disease
CPR	C-reactive protein
CRH	corticotropin-releasing hormone
ET-1	endothelin-1
HPA	hypothalamic-pituitary adrenal
IgE	immunoglobulin E
IL-6	interleukin-6
IR	ischemia-reperfusion
MC	mast cells
ME/CFS	myalgic encephalopathy/chronic fatigue syndrome
MI	myocardial ischemia
NGF	nerve growth factor
NT	neurotensin
NF-κB	nuclear factor-kappa B

PAF	platelet activating factor
ROS	reactive oxygen species
SP	substance P
TNF	tumor necrosis factor
UCP-2	uncoupling protein-2
Ucn	urocortin

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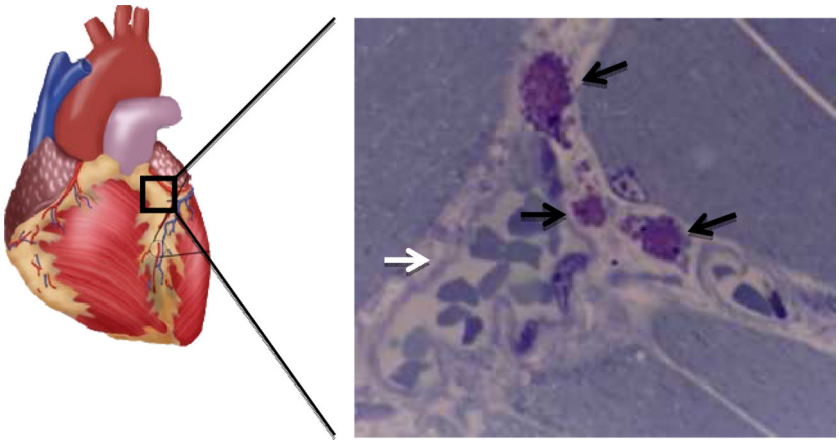

Figure 1.

MC (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 min. Magnification= x 400

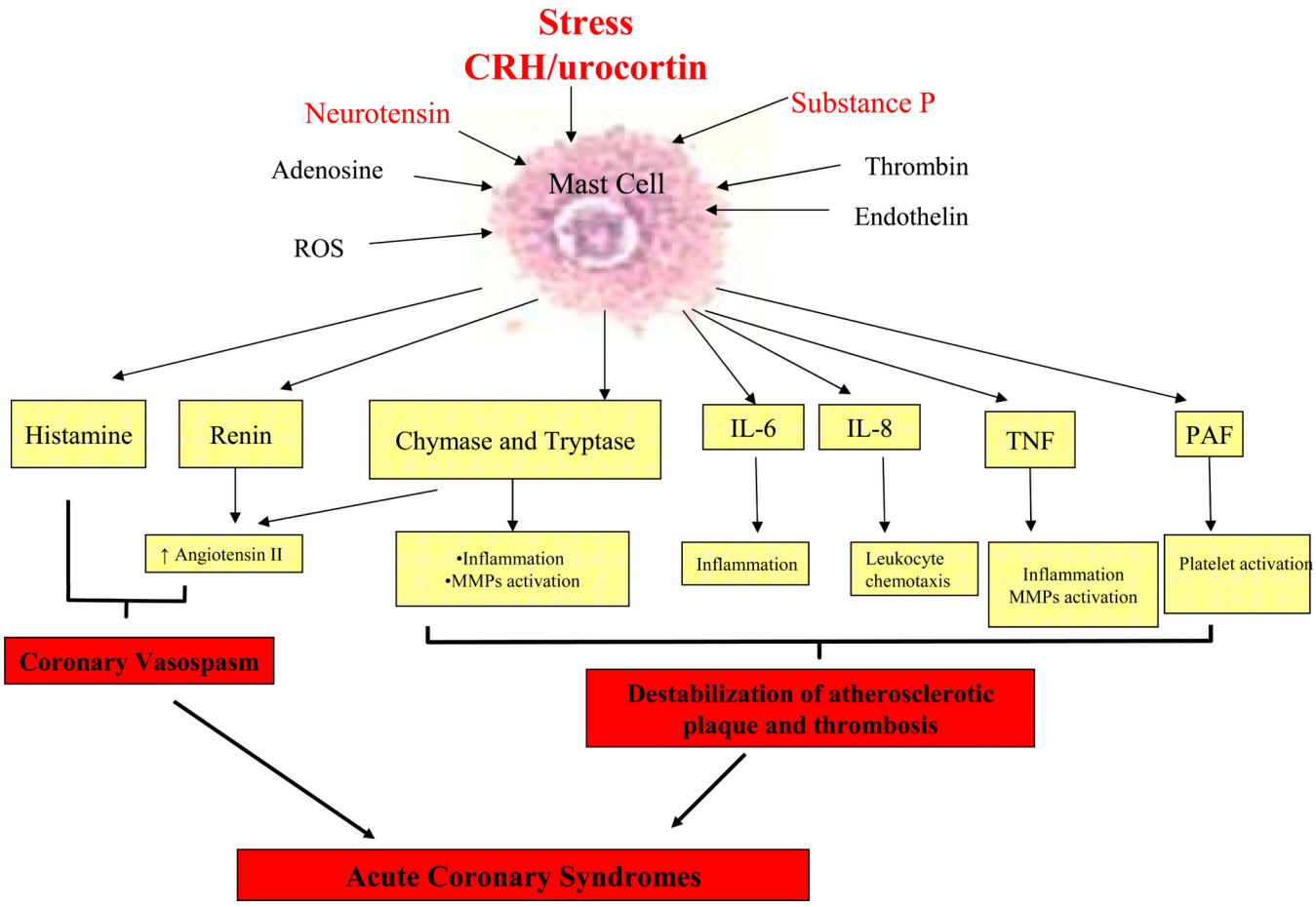

Figure 2.

Diagrammatic representation of the possible triggers of cardiovascular MC and their key mediators with CAD-relevant actions and major pathological sequellae.

Table 1

Mast cell mediators and their pro-ACS effects

Mediator	Cardiovascular effect
Chymase	Generates angiotensin II, vasoconstriction, MMP-1 activation, endothelial cell apoptosis, formation of foam cells
CRH	Autocrine MC and immune cell stimulation
Histamine	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 and deposition of LDL in the intima
IL-6	Pro-inflammatory, CRP induction, Th17 maturation, leukocyte recruitment
IL-8	Immune cell chemoattraction
Leukotrienes	Coronary vasoconstriction
MMP-9	Matrix and vascular integrity degradation
PAF	Platelet activation and aggregation, peo-inflammatory
Neurotensin	Pro-inflammatory, vasoconstriction
Thromboxanes	Platelet aggregation, vasoconstriction
Renin	Angiotensin I synthesis, vasoconstriction
TNF	Pro-inflammatory, IL-6 upregulation, MMP activation, endothelial cell apoptosis
Tryptase	Pro-inflammatory, PAR-2 activation, HDL degradation, endothelial apoptosis, induction of microvascular permeability and deposition of LDL in the intima
Ucn	Cardiomyocyte IL-6 release