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REVIEW

Stress-dependent control of cytokine production in mast cells stimulated through FcεRI and Toll-like 4 receptors

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Mast cells (MC) play an important role on allergic reactions initiated by the IgE/Antigen-dependent crosslinking of the high affinity IgE receptor (FcεRI). Also, their participation on inflammatory innate immune responses triggered by Toll-like receptors (TLRs) is now well documented. Physiological conditions such as stress exert a modulatory effect on allergic reactions since stress mediators activate signaling cascades that either interfere or potentiate FcεRI-dependent cytokine production. Moreover, the effect of stress mediators on cytokine production induced after TLR triggering has started to be addressed in this cell type. In a recent paper, we analyzed the effects of stress induced by forced swimming (FS) on the MC-dependent production of Tumor Necrosis Factor (TNF) induced by a single intraperitoneal injection of bacterial lipopolysaccharide (LPS) in mice. FS provoked an immediate and transient inhibition of LPS-elicited TNF accumulation in peritoneum, which lasted around to 30 min. With the aim to identify the mediator of stress responsible for the inhibition, we first blocked catecholamine release from adrenal glands (by adrenalectomy) or nerve terminals (with DSP4 treatment). With these manipulations we observed an important increase on basal i.p. NF levels and enhanced LPS-induced TNF release without any effect on stress-induced inhibitory effects. We then pre-treated animals with the glucocorticoid receptor antagonist mifepristone and did not observe any change on basal levels or stress-induced inhibition of TNF release. Finally, we administered an antagonist of acetylcholine receptors (mecamylamine) and observed an increase on basal levels of i.p. TNF values together with an important blockage of stress effects. Those results show for the first time that early MC-derived TNF secretion after Toll-like receptors is negatively controlled by adrenaline and transiently inhibited by the anti-inflammatory cholinergic reflex. Our results adds to the description of stress effects on MC activation and open new avenues in the research on the control of chronic inflammatory reactions associated with long term MC-dependent cytokine secretion

Keywords: Mast cells; stress; inflammation

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Introduction

Mast cells (MC) have been largely recognized as the initiators of allergic reactions [1]. After the crosslinking of the high affinity receptor for IgE (FcεRI), this cell type secrete numerous pro-inflammatory mediators which are concentrated on intracellular granules (such as histamine and proteases) or synthesized *de novo* (such as cytokines and araquidonic acid derivatives). In response to IgE/Ag complexes, MC secrete preformed mediators by a rapid process known as "degranulation", whereas exocytosis of cytokines triggered by other stimuli (such as bacterial

products) requires events that lead to slow piecemeal degranulation or activation of the constitutive secretory pathway [2]. Inflammatory mediators exert their effects on surrounding tissues, promoting vascular permeability changes, recruitment of leukocytes and pain generation. Although an initial deleterious role of MC activation was accepted, this concept changed with the discovery that MC can orchestrate protective inflammatory reactions against bacteria, parasites and tissue damage through the low-intensity triggering of the FcεRI by monomeric IgE, or the activation of Pattern Recognition Receptors (PRR) such as NOD, RIG and Toll-like receptors (TLRs) [3]. Also, non-regulated, long-term cytokine secretion by MC has been associated with distinct chronic-degenerative diseases [1].

The emerging role of MC as main controllers of the intensity of local inflammatory reactions triggered by stimuli of innate and adaptive immunity, and also as elements able to change the course of inflammation from a protective to deleterious outcome has lead to investigate the effect of stress on their activation.

During the stress response biochemical changes are induced in certain brain areas, notably in limbic areas, which converge at the activation of the hypothalamic-pituitary -adrenal axis (HPA)[4]. In those conditions, afferent sensory neurons activate sympathetic and parasympathetic pathways that trigger the production and release of glucocorticoids, corticotropin releasing hormone (CRH), vasopressin, substance P, neurotensin, adrenaline and acetylcholine, among others. Many of these mediators have direct effects on the activation of mast cells, either enhancing or suppressing responses to various stimuli activation of innate and adaptive immunity.

In some studies using mice subjected to physical and psychological stress, such as forced swimming (FS) or exposure to a predator, it has been shown that stress attenuates the production of pro-inflammatory cytokines in response to bacterial lipopolysaccharide (LPS) [5,6]. On the other hand, it has been described that various neuroendocrine mediators secreted during the stress response, such as corticotropin releasing factor (CRH), substance P and neurotensin increase degranulation of MC [7-9].

The following sections will describe some of the molecules relevant for cytokine secretion in MC stimulated through FcεRI and TLR4 receptors and the effects of stress mediators in cytokine production in this particular cell type.

Mast cells in adaptive immunity

MC constitute the main cell type involved in the initiation of type I hypersensitivity (allergic) reactions because they secrete inflammatory mediators after IgE/antigen (IgE/Ag) -dependent crosslinking of the FcεRI receptor. The FcεRI is a heterotetramer composed by an α subunit that binds to IgE, one β subunit that (in mice) is implicated in the amplification of the signal, and two γ subunits which initiate the signaling cascade. Both the β and γ subunits possess immunotyrosine activation motifs (ITAMs), which are phosphorylated by Src family kinases, such as Lyn and Fyn.

Receptor activation promotes the phosphorylation and recruitment of some adapter molecules such as linker of activation of T cells (LAT), Grb2-associated binder-like protein 2 (Gab2), Src homology 2 master-containing leukocyte phosphoprotein of 76 kDa (SLP-76) and others. Those adapters, in turn, allow the recruitment and activation of effector proteins such as phospholipase C (PLC), phosphoinositide 3-kinase (PI3K), and small GTPases. PLC hydrolyzes the phosphatidyl inositol 4,5-biphosphate (PI4,5-P2) producing inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 binds to IPR receptors in the endoplasmic reticulum and generates calcium depletion in this compartment, while the DAG is responsible for activating the classical isoforms of PKC, event required for degranulation. Phospholipase A induces the formation of arachidonic acid derivatives and small GTPases lead to the activation of mitogen-activated protein (MAPK) that stimulate some transcription factors to promote de *novo* synthesis of cytokines [10-12] (Figure 1).

Activation of the FcεRI signaling system is related to type I hypersensitivity reactions, such as those involved in asthma and atopic dermatitis. In those cases, inflammatory mediators secreted by the FcεRI signaling system leads to bronchoconstriction, increased vascular permeability and vasodilation [13, 14].

Mast cells and innate immunity

MC express pattern recognition receptors (PRRs) such as the Toll-like 4 receptor. TLR4 activation is associated to the activation of transcription factors (specially NFκB) to induce *de novo* cytokine synthesis and their secretion by the constitutive pathways, but also induce release of preformed mediators by a mechanism known as piecemeal degranulation [13]. The most studied ligand for TLR4 receptor in MC is the lipopolysaccharide (LPS) from Gram-negative bacteria.

The intracellular response to LPS in MC is initiated by the TLR-4 dependent recruitment of the adapter protein MyD88 (since the activation of MyD88-independent pathways has not been reported in this cell type). After this, the TRAF6

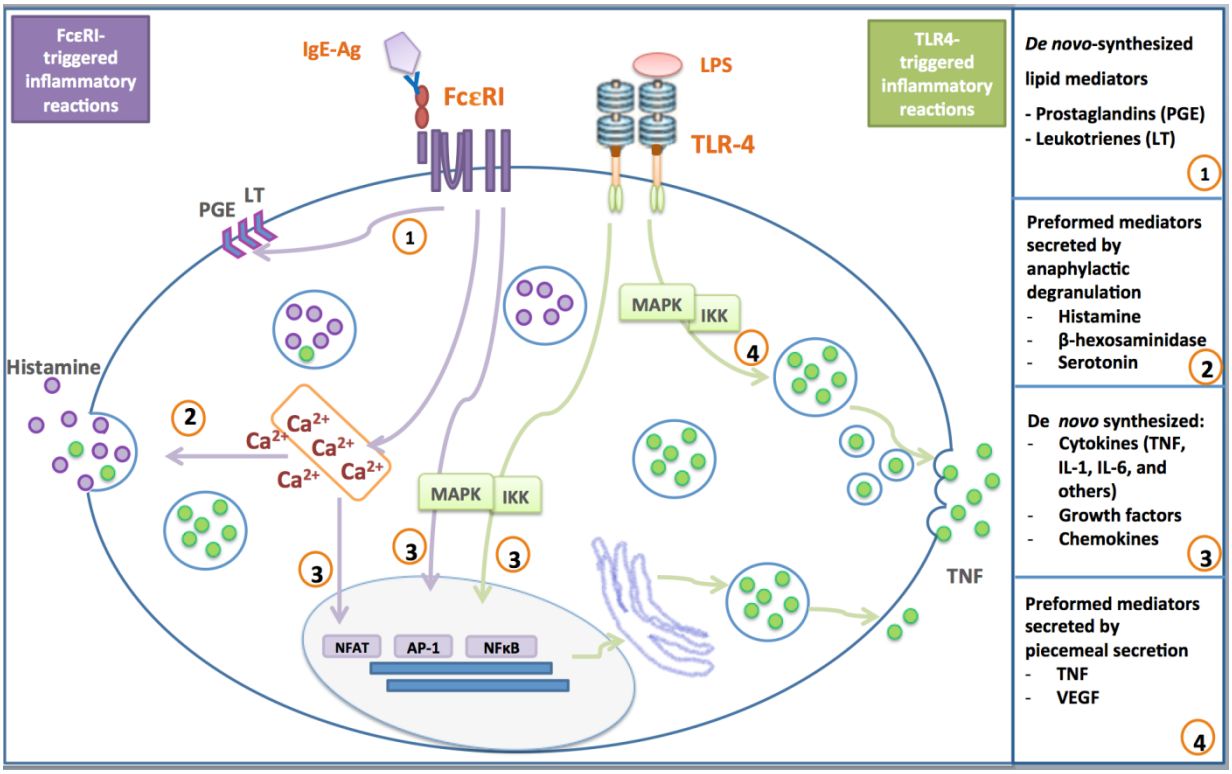

Figure 1. Main signaling routes connecting FcεRI or TLR4 receptors with cytokine production in MC. Upon stimulation of the FcεRI signaling cascade with IgE/Ag complexes, distinct pathways are activated to connect the receptor with the production of arachidonic acid (1), secretion of the pre-formed content of granules (2) and *de novo* synthesis of cytokines trough transcription of specific genes and mRNA stabilization (3). After activation of TLR4 receptor, a pathway inducing the activation of various transcription factors to produce the synthesis of pro-inflammatory cytokines is turned on (3), but selective exocytosis of granule content (such as TNF) is also observed (4).

ubiquitin ligase leads to TAK1 phosphorylation, and TAK1 bifurcates the signal transduction system on two main branches: one leading to the activation of MAP kinases (ERK, p38 and JNK) and the IKK-dependent activation of NFκB.

Recent studies from our laboratory indicate that IKK and ERK phosphorylation are directly related to the process of TNF secretion in mast cells. The IKK inhibitor BAY11-7085 was able to reduce the secretion of TNF in bone marrow-derived mast cells (BMMCs) stimulated with LPS. Also, the MEK inhibitor PD98059 prevented TNF secretion in response to LPS [16]. A closer analysis has shown that IKK activation promotes the phosphorylation of membrane SNARE proteins involved in cytokine secretion, such as SNAP-23[17], but the specific role of ERK is still unknown (Figure 1).

In vivo, there are several mouse models used to study the innate response after stimulation of the TLR-4 receptors in MC, among them, the cecal ligation and puncture (CLP) model involves tying a section of intestine (caecum) with its posterior perforation. This allows resident bacteria to invade the entire peritoneal cavity initiating the systemic response to sepsis [18]. Other models are used to investigate the response mounted only to endotoxin and they consist on the direct injection of purified LPS to peritoneal cavity [19, 20]. Using those models in WT and MC-deficient (*Kit* $^{Wv/Wv}$ *and Kit* $^{Wsh/Wsh}$) mice, it has been shown that resident MCs are responsible for the early production of TNF during the first two hours after TLR-4 stimulation [19, 21, 22].

In vitro models of TLR4-dependent activation of MC consist in the direct stimulation of BMMCs or MC cell lines (such as rat RBL 2H3 cells or human LAD-2 cell line) with TLR4 ligands. Using those cellular models and accordingly to the well-documented mast cell heterogeneity, it has been shown that MC response to LPS depends on cell preparation and culture conditions [23-25]. For example, in BMMC, TLR4 stimulation with LPS (500 ng/ml) induces secretion of TNF at short times (1 to 4 hours) [24,16] whereas RBL-2H3 cells it takes a long-lasting stimulation (6 to 12 h) with high LPS concentrations (1 μg/mL) to observe an increase on TNF production.

TLR receptors are activated also after the recognition of damage-associated molecular patterns (DAMPs), such as heat shock proteins [26], β-defensins, fibronectin, hyaluronic

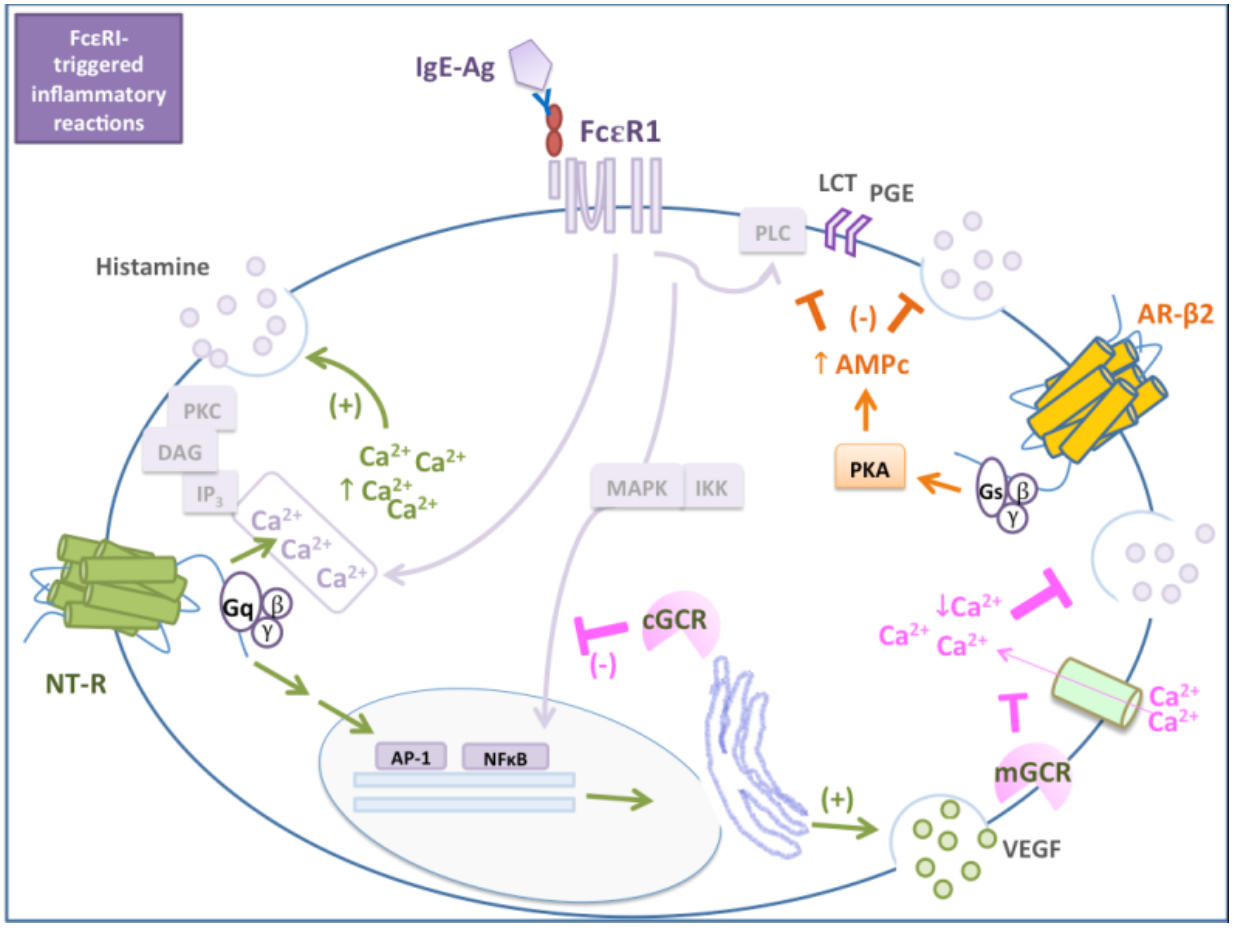

Figure 2. Modulation of FcεRI-dependent responses by stress hormones in MC. IgE/Ag-induced degranulation and cytokine synthesis is positively affected by neurotensin receptors (NT-R) by a mechanism depending on calcium mobilization and activation of specific transcription factors. Those pro-inflammatory signals are negatively controlled by the activation of β2-adrenergic (AR-β2) receptors and cytoplasmic or membrane glucocorticoid receptors (c and m GCR). AR-β2 and GCR also interfere with the activation of calcium channels and enzymes responsible for the production of lipid-derived inflammatory mediators (see text for details).

acid, β-amyloid peptide [24], and fatty acids [28]. Recent evidence indicates that in chronic-degenerative diseases, those agents could be responsible for TLR receptors triggering on MC surface. For example, in the case of rheumatoid arthritis, local and long-lasting inflammatory reactions eventually lead to destruction of cartilage and bone. In this process, the damage sinovium produce DAMPs such as fibronectin, which activate MC similarly to what occurs with LPS. MC, in turn, contribute to the increased inflammatory response in the damaged tissue [29].

Mediators of stress and its effects on the activation of mast cells

HPA activation induces the production of CRH in the paraventircular nuclei of the hypothalamus. This hormone travels through the pituitary portal and promotes ACTH production in the anterior pituitary. On the other hand, in the adrenal cortex promotes the production of glucocorticoids. Some of the secreted mediators during activation of the HPA axis may *per se* induce cytokine release from MC but also can modify their response to stimulation of TLR and FcεRI receptors by a mechanism that has not been fully described (Figures 2 and 3).

Corticotropin-releasing hormone (CRH)

CRH is a peptide synthesized in response to stress in paraventricular nucleus of the hypothalamus. However, at the periphery, other cell types such as MC are able to synthesize it [30]. CRH acts through its G-protein-coupled receptors (GPCRs), CRH-R1 and CRH-R2. When activated, their signaling cascades increase intracellular concentrations of cAMP by action of Adenylyl cyclase (AC), and, eventually, activate protein kinase A (PKA) [31].

The immobilization stress model has been widely used to generate acute stress in rats and mice. This model consists on

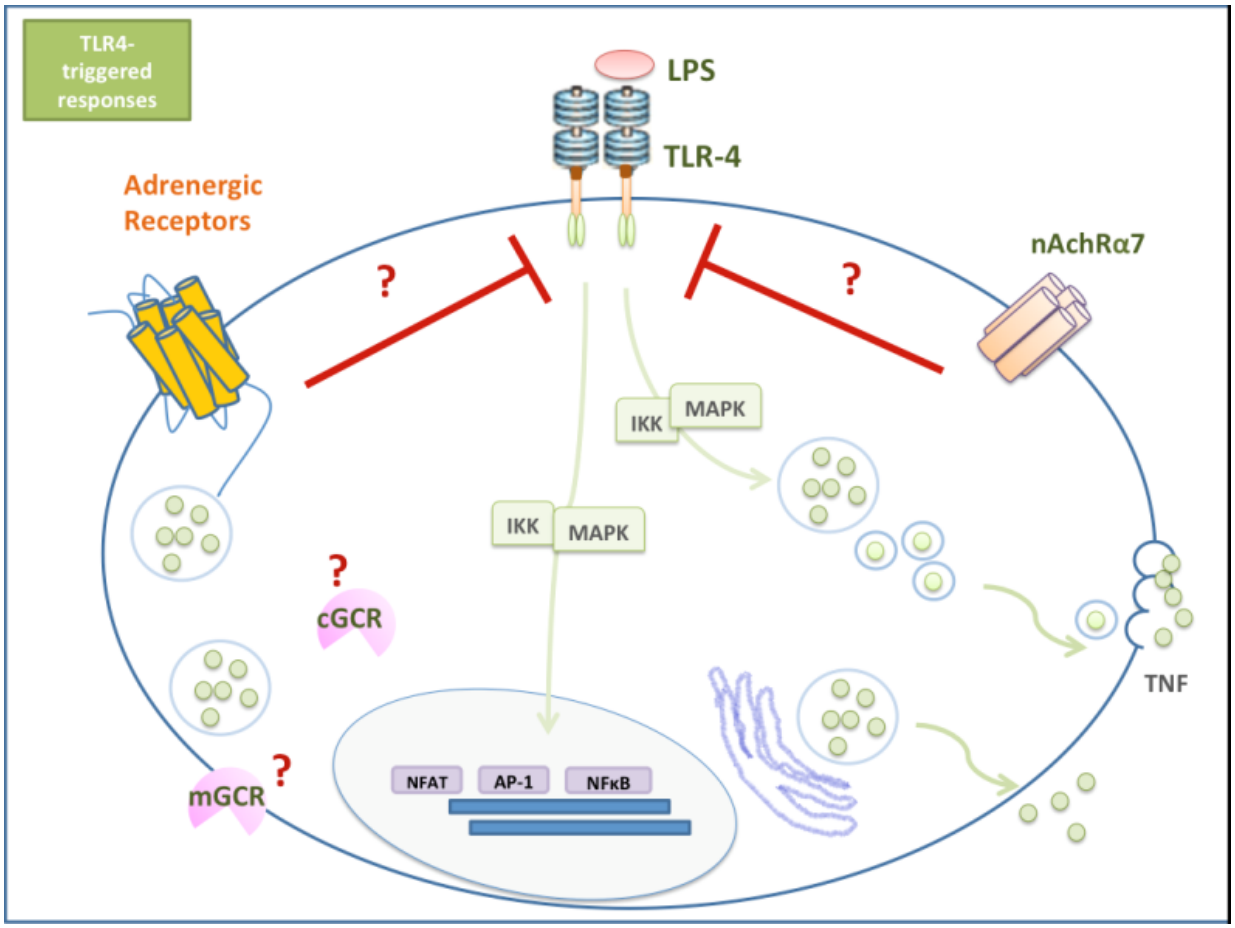

Figure 3. Modulation of TLR4-dependent responses by adrenergic and nicotinic α7 acetylcholine (nAchRα7) receptors. In murine peritoneal cavity, MC-dependent production of TNF after LPS addition in is negatively controlled by adrenaline (secreted by adrenal glands or by peripheral nerve terminals) and by acetylcholine released after swim stress. Molecular mechanisms behind this inhibition remain to be described (see text for details).

the introduction of the animal into a cylinder designed accordingly to prevent movement of scape of the experimental subject. Under those conditions, it has been shown that stress induces intracranial and skin degranulation of MC in the rat. MC degranulation was not observable when animals were pre-treated with and anti-CRH serum prior to immobilization [7, 9].

The presence of CRH-1 and CRH-2 receptors has been reported in a human leukemia mast cell line (HMC-1). Activation of these cells with CRH selectively promoted the secretion of VEGF, but not tryptase, histamine or certain other cytokines. The increased secretion of VEGF was associated with the activation of AC and PKA, since VEGF secretion was increased with froskolin and inhibited with SQ22536 (an inhibitor of AC) or the CRH-1 antagonist alarmin [32]. CRH acting on the CRH-R1 induces phosphorylation of P-38 MAPK, but not ERK or JNK in MC [33]. Similar studies, performed with the human mast cell line LAD-2, have found that secretion of CRH enhances VEGF production induced after activation of FcεRI [34].

Glucocorticoids

Glucocorticoids are the best-studied mediators released after stress responses. Their actions on the immune response have been extensively characterized and generally lead to the suppression of inflammation, reason by which they are wide prescribed for the treatment of multiple diseases such as asthma and distinct types of allergies.

Glucocorticoids have anti-inflammatory effect by acting on their receptors that, without any stimulus, are localized in the cytoplasm (cGCR) forming complexes with chaperone proteins such as the 90 kDa heat shock protein (Hsp90). After binding of the ligand, the complex dissociates and cGCR protein is transported to cell nucleus where it binds to hormone response elements on DNA, inducing the transcription of genes that interfere with the activation of the transcription factor NFκB such as IκB [35-37]. In MC isolated from dexamethasone-treated animals or in dexamethasone-treated BMMCs [38, 40] a reduction on the secretion of preformed mediators such as β-hexosaminidase,

serotonin and certain arachidonic acid derivatives was observed [40]. The molecular mechanism behind the blockage on the secretion of pre-formed mediators in MC has not been fully described but some experiments in RBL-2H3 cells indicate that a pre-incubation with corticosterone causes an inhibition on the rise on intracellular calcium current $[Ca^{2+}]I$, which is necessary for histamine release [41].

We have reported that the inhibitory effects of swim stress on MC-dependent, LPS-induced TNF secretion in peritoneal cavity were not prevented by pretreatment with mifepristone (a commonly used antagonist of GR) despite the important increase on corticosterone plasma levels observed [6]. Our results suggest that GR exerts a marginal control on TNF secretion stimulated by TLR4 receptors in MC.

Finally, membrane glucocorticoid receptors (mGCR) have been found in a number of immune cells and their activation causes changes in basic properties of plasma membrane, affecting intracellular concentrations of Ca^{2+}, ATP and cAMP [42, 43]. Also, changes on membrane localization of mGCR were detected in RBL-2H3 cells after IgE/antigen stimulation [44].

Catecholamine

During the stress response, adrenaline and noradrenaline are secreted by chromaffin cells located in the adrenal medulla by a process dependent on acetylcholine release. Those catecholamines activate with different affinities three subtypes of G-protein coupled receptors known as adrenoceptors α_1, α_2 and β (1, 2, 3). β2-adrenergic receptor is positively coupled to Gs protein and promotes the activation of AC, resulting in the intracellular increase of cAMP levels. MC express this receptor subtype and has been widely studied because its activation modulates the main inflammatory reaction associated to asthma [45, 46]. In an study conducted in 2001 by Graveskaya *et al* [47] peritoneal MC purified from rats exposed to cold stress (inmersion of animals for 5 min in a water bath at 4 ℃) were stimulated with the calcium ionophore A23187 or the secretagogue compound 48/80. Authors found that stress inhibited A23187-induced histamine release and same effect was observed when, instead of exposing rats to stress, were administered with epinephrine. Other *in vivo* studies have reported that treatment with isoproterenol and clembuterol (two different β-adrenergic agonists) decreases the skin anaphylactic reaction and the IgE/Ag-induced peritoneal histamine secretion [48]. On the other hand, studies in MC isolated from lung or intestine reported a decrease in the secretion of histamine, leukotrienes and prostaglandins when cells were pre-incubated with β-adrenergic agonists [46, 48-51].

Some molecular events have been proposed to explain the inhibitory effects that AR-β2 stimulation exerts on the FcεRI signaling system. It is known, for example, that an increase on cAMP is required for the phenomenon, since incubation with forskolin mimics the inhibitory effects of β-adrenergic agonists [52]. Also, it has been shown that the adrenergic inhibition is prevented when cells are simultaneously incubated with cholera toxin, experiment that confirms the participation of Gs. It has also been reported that the β2-AR agonist salbutamol inhibits calcium currents evoked by FcεRI triggering in an event that involves the blockage of potassium channels activity ($iK_{Ca}1$) necessary for mast cells degranulation [53].

Adrenalectomy importantly increased basal and LPS-triggered levels of TNF in the peritoneal cavity of mice, an effect also observed after pharmacological lesion of the noradrenergic system with the specific neurotoxin DSP-4. However, any of those manipulations altered the deletereous effects of swim stress [6], suggesting that catecholamines maintain an inhibitory tone on the peritoneal amount of TNF but do not alter the acute effects of stress on that parameter.

Neurotensin

Neurotensin (NT) is a peptide secreted at nerve terminals in response to tissue injury or pain. Acting on its G-coupled receptor (NT-R), this hormone directly activates MC and induces the secretion of β-hexosaminidase and histamine and enhances the response to IgE/Ag [54, 55]. NT also increases the expression of VEGF mRNA and CRH, phenomena related to the increase in intracellular Ca^{2+} and the activation of the transcription factor NFκB [9]. Elevated levels of NT have been found in serum of patients of psoriasis, phenomenon that may explain why some psoriasis patients worsening when subjected to stress [56]. In addition, it has been reported that acute restraint stress increases cardiac degranulation mast cells and that the effect is blocked when the animals are pre-administered with an antagonist to NT-R [57, 58]. This phenomenon could be relevant in the development of chronic cardiovascular diseases.

Acetylcholine

During the stress response, cholinergic pathways innervating diverse regions of the limbic system are activated [59-61]. Acetylcholine causes the release of catecholamines in the adrenal medulla and acts directly on their muscarinic and nicotinic receptors located on the plasma membrane of many cells of the immune system, thereby modulating inflammatory responses. The mechanisms by which acetylcholine modulates inflammation have been widely described over the past decades generating the discovery of

an inhibitory pathway known as the cholinergic anti-inflammatory reflex. Cholinergic anti-inflammatory reflex is composed by a set of interactions that take place between the immune cells and nerve terminals. When inflammation starts in certain location, cytokines and mediators secreted by immune cells activate its specific receptors on vagal afferent nerve terminals. This signal is integrated into the CNS, in the nucleus of the solitary tract and the hypothalamus, causing that the efferent vagal terminals of the celiac ganglion secrete acetylcholine that promotes secretion of catecholamines. Released catecholamines act on β-adrenergic receptors in resident T cells in the spleen. These cells produce and release acetylcholine that inhibits the production of pro-inflammatory cytokines to activate the receptors nAchRα7 on adjacent spleen macrophages [62].

The inhibitory downstream events triggered by the activation of nAchRα7 receptors have been described primarily in macrophages, however, some studies have also been made in other cell types such as mast cells and microglia [63, 65]. In general, it is known that nAchRα7 activation induces recruitment of molecules such JAK and STAT, which inhibit the activity of the transcription factor NFκB [66]. In rodent models of endotoxemia it has been seen that electrical stimulation of the vagus nerve attenuates proinflammatory cytokine concentrations in serum and also prevents the development of endotoxic shock [67].

The anti-inflammatory effects of acetylcholine have been demonstrated in other in vivo models of inflammation. In our study, we observed that the inhibitory effect evoked by stress can be prevented by treating mice with the nicotinic antagonist mecamylamine [6]. These results suggest that acetylcholine released in response to stress activate nicotinic receptors on MC and inhibit MC responses to LPS. In vitro studies have demonstrated the presence of nicotinic receptors in BMMCs [68-69]. In RBL-2H3 cells, the effect of nicotinic agonists such as nicotine and GTS-21 has been evaluated and results indicate that the nicotinic agonist can inhibit the production of leukotrienes, β-hexosaminidase and histamine induced by FcεRI activation [70]. Despite the importance that PAMP and DAMP-induced cytokine synthesis by MC has on the development of chronic inflammatory conditions, the molecular mechanisms of inhibition mediated by stress are still far from being described (Figure 3).

Conclusions

Stress mediators induce important modifications to MC responses to stimuli from the innate and the adaptive immune system. Some of those mediators show a positive effect on the response triggered by the FcεRI, such as CRH and substance P, while other exert negative effects, such as glucocorticoids, catecholamines and acetylcholine. In contrast, the existing information about the effects of stress mediators on MC-dependent cytokine synthesis after stimulation of TLR receptors is scarce. Our recent findings reporting the transient inhibitory role of stress on the TLR4-dependent cytokine production in MC through the activation of the anti-inflammatory reflex open new avenues in the identification of therapeutic targets for chronic-degenerative diseases in which long-term production of cytokines associated to MC activation is related with progressive tissue damage.

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Conflict of interest

The authors have no financial or academic conflicts of interest

List of abbreviations

AC: adenylyl cyclase; ACTH: adrenocorticotropic hormone; Ag: antigen; AP-1: activation protein 1; AR-β2: β2-adrenergic receptor; ATP: adenosine triphosphate; BAY11-7085: (E)-3-(4-t-butylphenylsulfonyl)-2-propenentrile; BMMC: bone marrow-derived mast cells; cAMP: cyclic AMP; CNS: central nervous system; CRH: corticotropin releasing hormone; DAG: diacyl glycerol; DAMP: damage-associated molecular pattern; DSP-4: N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine; ERK: extracellular signal regulated kinase; FcεRI: high affinity receptor for IgE; FS: forced swimming; Gab2: Grb2-associated-binding-protein 2; GCR: glucocorticoid receptor; GTS-21: 3-(2,4-Dimethoxybenzylidene)-anabaseine dihydrochloride; HPA: hypothalamic-pituitary-adrenal axis; IKK: inhibitor of nuclear factor kappa B kinase; inositol triphosphate; IgE: immunoglobulin E; IPR: IP3 receptor; ITAM: immunoreceptor-tyrosine-based-activation motif; JAK: Janus kinase; LAT: linker of activation of T cells; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; MC; mast cells; MEK: MAPK kinase; MyD88: myeloid differentiation primary response 88; nAchRα7: α7 nicotinic acetylcholine receptor; NFκB: nuclear factor κ-light chain enhancer of activated B cells; NOD-like: nucleotide oligomerizarion domain-like receptors; NT: neurotensin; p38: MAPK of 38 kDa; PAMP: pathogen-associated molecular pattern; PD98059: 2-(2-Amino-3-methoxyphenyl)-4H-1

benzopyran-4-one; PI3K: phosphatidylinositol 3 kinase; PKA: protein kinase A; PLC: phospholipase C; PRR: pattern recognition receptors; RIG-like: retinoid acid-inducible gene 1-like receptors; SLP76: SH2 domain containing lymphocyte protein of 76 kDa; SNAP-23: synaptosomal-associated protein 23; SNARE: soluble NSF attachment protein receptor; STAT: signal transducer and activator of transcription; TAK-1: transforming growth factor β-activated kinase 1; TLR: toll-like receptor; TNF: tumor necrosis factor.

Author contributions

FGM carried out most of the bibliographical search and prepared the first draft of the manuscript and figures; CLR contributed with the analysis of the different rodent models used on stress research and corrected the first draft of the manuscript; CGE design the manuscript, suggested bibliography and corrected the different versions of figures and text until its final version.

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