

Review article

# Critical role of mast cells in inflammatory diseases and the effect of acute stress

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## Abstract

Mast cells are not only necessary for allergic reactions, but recent findings indicate that they are also involved in a variety of neuroinflammatory diseases, especially those worsened by stress. In these cases, mast cells appear to be activated through their Fc receptors by immunoglobulins other than IgE, as well as by anaphylatoxins, neuropeptides and cytokines to secrete mediators selectively without overt degranulation. These facts can help us better understand a variety of sterile inflammatory conditions, such as multiple sclerosis (MS), migraines, inflammatory arthritis, atopic dermatitis, coronary inflammation, interstitial cystitis and irritable bowel syndrome, in which mast cells are activated without allergic degranulation.

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## 1. Selective release of mast cell mediators

Mast cells derive from a distinct precursor in the bone marrow (Rodewald et al., 1996) and mature under local tissue microenvironmental factors (Galli, 1993). Mast cells are necessary for the development of allergic reactions, through crosslinking of their surface receptors for IgE (FcεRI), leading to degranulation and the release of vasoactive, pro-inflammatory and nociceptive mediators that include histamine, cytokines and proteolytic enzymes (Kobayashi et al., 2000; Galli et al., 2002). The multitude of mediators that could be secreted has given rise to new speculations about the possible role of mast cells in immune responses (Gurish and Austen, 2001), whether it is acquired immunity (Marone et al., 2002) or in response to bacteria (Malaviya and Abraham, 2001). As the spectrum of diseases that may involve mast cells increases, so do the questions concerning the triggers and the mechanisms through which

mast cells may be able to participate in such diverse conditions without the “classic” degranulation by exocytosis typical of anaphylactic reactions.

A main aspect of mast cell physiology that had been largely ignored until recently is that mast cells can secrete mediators without overt degranulation (Theoharides and Douglas, 1978), through differential or selective release (Theoharides et al., 1982), this process is probably regulated by the action of distinct protein kinases on a unique phosphoprotein (Theoharides et al., 1980; Sieghart et al., 1978).

Unlike allergic reactions, mast cells are rarely seen to degranulate during autoimmune (Benoist and Mathis, 2002) or inflammatory processes (Woolley, 2003); moreover, the “mast cell stabilizer” disodium cromoglycate (cromolyn) may be ineffective as a therapeutic modality (Okayama et al., 1992). Instead, mast cells appear to undergo ultrastructural alterations of their electron dense granular core indicative of secretion, but without overt degranulation, a process that has been termed “activation” (Dimitriadou et al., 1990; Dimitriadou et al., 1991; Theoharides et al., 1995a) “intra-granular activation” (Letourneau et al., 1996) or “piece-meal” degranulation (Dvorak et al., 1992a,b). Such “subtle” activation may be associated with the ability of mast cells to release some mediators selectively (Kops et al.,

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Table 1  
Neuroinflammatory diseases involving mast cells<sup>a</sup>

Disease	Pathophysiological effects
Asthma	Bronchoconstriction, pulmonary inflammation
Atopic dermatitis	Skin vasodilation, T cell recruitment, inflammation, itching
Cardiovascular disease	Coronary inflammation
Chronic prostatitis	Prostate inflammation
Fibromyalgia	Muscle inflammation
Irritable bowel syndrome	Smooth muscle and myenteric plexus irritation
Interstitial cystitis	Bladder mucosal damage and inflammation
Migraines	Meningeal vasodilation and inflammation
Multiple sclerosis	Increased BBB permeability, brain inflammation
Neurofibromatosis	Skin nerve growth, fibrosis
Osteoarthritis	Articular erosion and inflammation
Rheumatoid arthritis	Joint inflammation, cartilage erosion
Scleroderma	Skin inflammation and fibrosis

<sup>a</sup> Many of these conditions coexist in the same patients.

1984, 1990; Van Loveren et al., 1984), as shown for serotonin (Theoharides et al., 1982), eicosanoids (Benyon et al., 1989; Levi-Schaffer and Shalit, 1989; van Haaster et al., 1995) and IL-6 (Leal-Berumen et al., 1994; Marquardt et al., 1996; Gagari et al., 1997; Hojo et al., 1996). In fact, we recently showed that interleukin-1 (IL-1) can stimulate human mast cells to release IL-6 selectively without degranulation, through a unique process utilizing 40–80-nm vesicles unrelated to the secretory granules (800–1000 nm) (Kandere-Grzybowska et al., 2003b).

These findings suggest that mast cells may also be involved in inflammatory diseases (Theoharides, 1996) that include multiple sclerosis (MS) (Theoharides, 1990), migraines (Theoharides, 1983), arthritis (Woolley, 1995), cardiovascular disease (Constantinides, 1995), interstitial cystitis of the urinary bladder (Theoharides and Sant, 1994), and irritable bowel syndrome (IBS) (Weston et al., 1993). In fact, many of these diseases (Table 1) appear to occur concomitantly, as in interstitial cystitis (Kozioł et al., 1993; Alagiri et al., 1997).

## 2. Brain inflammation and MS

Stress is a basic response to diverse real or perceived threatening stimuli. It activates the hypothalamic–pituitary–adrenal (HPA) axis through secretion of corticotropin-releasing hormone (CRH or CRF for factor) that normally suppresses immune responses (Habib et al., 2001). However, CRH has also been shown to promote inflammation (Karalis et al., 1991; Chrousos, 1995). Increasing evidence indicates that symptoms in relapsing–remitting multiple sclerosis (MS) may be precipitated or exacerbated by acute stress (Mei-Tal et al., 1970; Warren et

al., 1982; Goodin et al., 1999; Mohr et al., 2000; Ackerman et al., 2002). In view of the fact that blood–brain barrier (BBB) disruption is known to precede many pathological or clinical symptoms of MS (De Vreis et al., 1997; Johnson et al., 1988; Theoharides et al., 1993; Kwon and Prineas, 1994), it is of interest that brain mast cells are activated by acute stress (Rozniecki et al., 1999) leading to increased BBB permeability (Rozniecki et al., 1999; Esposito et al., 2002). This effect was absent in mast cell deficient mice (Esposito et al., 2002). Stress-induced increase in BBB permeability involved mast cell activation by CRH (Esposito et al., 2002). Brain mast cells have been characterized (Pang et al., 1996a) and shown to be located close to CRH-positive neurons (Theoharides et al., 1995b). CRH could influence BBB integrity either by stimulating brain mast cells, since mast cells can express CRH-1 receptors (Theoharides et al., 1995b, 2003), or by affecting brain microvessels directly (Esposito et al., 2003).

Evidence that stress disrupts the BBB in rats had been published previously (Belova and Jonsson, 1982; Sharma et al., 1991, 1995; Skultetyova et al., 1998). For instance, an increase in BBB permeability in response to short-term forced swimming was shown to occur in the cerebellum, the thalamus and the hypothalamus (Sharma et al., 1991). Moreover, the mast cell secretagogue, compound 48/80, has been shown to stimulate brain mast cells in rats (Dimitriadou et al., 1990) and to increase BBB permeability in pigeons (Zhuang et al., 1996). Acute stress also led to BBB disruption and shortened the time of onset of experimental allergic encephalomyelitis (EAE) in (Chandler et al., 2002) a model system for the study of MS.

EAE was attenuated and delayed in W/W<sup>v</sup> mast cell deficient mice (Secor et al., 1991), but was fully restored upon mast cell reconstitution even in the absence of brain mast cell replenishment (Brown et al., 2002). This finding suggests a possible indirect role of mast cells in the pathophysiology of EAE, possibly by regulating the permeability of the BBB (Theoharides, 1990). In fact, both activating and suppressing Fc receptors were recently shown to be expressed on mast cells and regulate EAE disease severity in mice (Robbie-Ryan et al., 2003). The development of EAE had previously been shown to involve mast cell accumulation in the rat (Dimitriadou et al., 2000) that could be due to chemotactic activity elicited by RANTES (Conti et al., 1998) or MCP-1 (Conti et al., 1997) secreted from either glial cells or infiltrating leukocytes. Immunocytochemistry with rat mast cell protease (RMCP)-specific antibodies and in situ hybridization showed that the EAE-associated increase in brain mast cells was mostly due to RMCP-II containing or immature mast cells that did not appear degranulated (Rouleau et al., 1997). In this context, it is important to note that monkey EAE was recently shown to be associated with ultrastructurally evident intragranular brain mast cell activation without overt degranulation (Letourneau et al., in press).

Mast cells have also been reported in MS plaques (Olsson, 1974; Krüger et al., 1990; Toms et al., 1990; Ibrahim et al., 1996) and could participate in demyelination directly (Theoharides et al., 1993; Brenner et al., 1994). Fig. 1 suggests possible pathophysiologic events derived from mast cell activation in the brain. For instance, myelin basic protein activated mast cells leading to brain demyelination (Theoharides et al., 1993), and both this action, as well as that of compound 48/80 (Vliagoftis et al., 1992) and of carbachol (Spanos et al., 1996) were shown to be enhanced by estradiol. These findings could be important in view of the fact that mast cells express estrogen receptors (Pang et al., 1995a; Zhao et al., 2001) and MS occurs more often in women. In this regard, it is noteworthy that the unique mast cell protease tryptase (Rozniecki et al., 1995) and histamine (Tuomisto et al., 1983) were elevated in the CSF of MS patients. Gene microarray analysis of MS plaques revealed increased expression of the mast cell related products 5-lipoxygenase in acute lesions, as well as histamine-type 1 receptor and the FcεRI receptor in chronic lesions (Tompkins and Miller, 2002). Most notable was the upregulation of nuclear factor IL-6 (Lock et al., 2002), especially since we recently showed that acute stress induced increases in serum histamine (Huang et al., 2002a,b) and IL-6 (Huang et al., 2003), both of which were entirely mast cell dependent. Such findings have led to recent re-affirmation of mast cell involvement in diseases of the nervous system (Dines and Powell, 1997; Pedotti et al., 2003). A recent review also hypothesized that mast cells may serve as possible targets for MS therapy (Tompkins and Miller, 2002).

In this context, it is critical that the histamine/serotonin receptor antagonist, cyproheptadine, and the mast cell activation inhibitor, proxicromil, have been reported to inhibit EAE (Dietsch and Hinrichs, 1991). Moreover, the histamine-1 receptor antagonist, hydroxyzine inhibited EAE (Dimitriadou et al., 2000) and also reduced brain mast cell activation (Dimitriadou et al., 2000). Hydroxyzine was also recently shown to reduce symptoms of MS in a double-blind, placebo-controlled pilot clinical trial (Theoharides et al., 2002).

### 3. Meningeal inflammation and migraines

Migraine headache is still a descriptive term that has been used primarily to refer to the brain and is usually associated with meningeal and cerebral vasodilation, as well as “spreading” neuronal depression (Spierings, 2003). It was hypothesized that mast cells may be involved in the pathophysiology of migraines (Theoharides, 1983). Mast cells are located in close apposition to neurons in the meninges (Dimitriadou et al., 1987; Rozniecki et al., 1999) and can be activated by neuropeptides (Goetzl et al., 1985, 1990; Foreman, 1987; Church et al., 1989), by antidromic nerve stimulation (Dimitriadou et al., 1991, 1992), as well as by acute immobilization stress (Theoharides et al., 1995a,b). Brain mast cells activated by acute stress lead to increased vascular permeability (Esposito et al., 2001), an effect dependent on mast cells and CRH (Esposito et al., 2002).

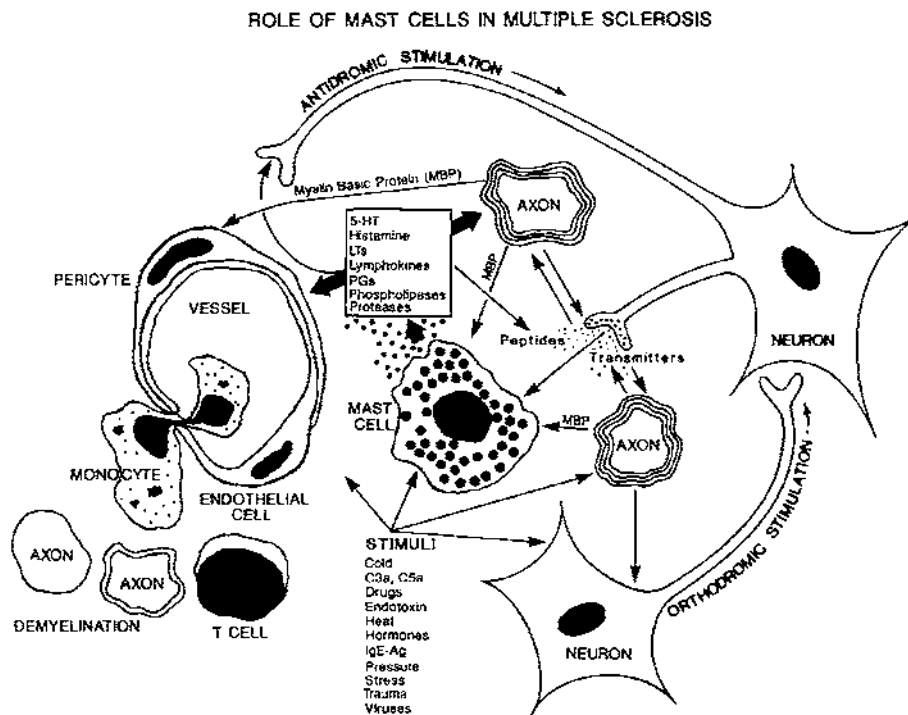


Fig. 1. The brain mast cell is depicted as having a key role in the pathogenesis of MS by regulating the permeability of the BBB and participating in demyelination, in response to a variety of endogenous and exogenous triggers.

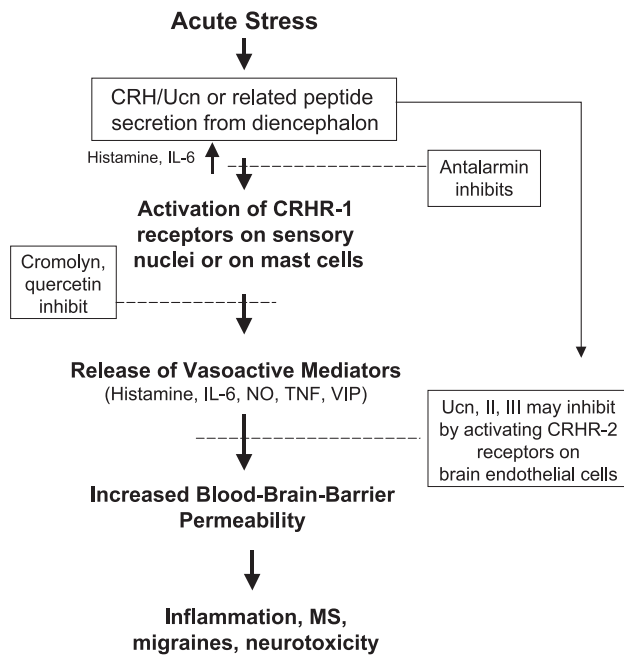


Fig. 2. Schematic representation of the sequence of events that may lead to mast cell activation BBB permeability, and neurogenic inflammation in response to acute stress.

Stress is known to precipitate or exacerbate migraines, raising the possibility of some underlying pathologic mechanism. One such possibility comes from the study of children migraineurs, in whom the frequency and severity of migraines was reduced, along with the unique mast cell biochemical marker tryptase, when they were taught relaxation techniques (Olness et al., 1999). Recent studies have shown that stress-induced neurogenic inflammation depends on NK-1 receptors, but does not require substance P (SP) (Kandere-Grzybowska et al., 2003a), while it may involve a direct action of CRH on brain microvessels (Esposito et al., 2003). Yet, delayed responses may also involve IL-6 and nitric oxide elevations in dura macrophages (Reuter et al., 2001). These findings have led to a new model for the pathogenesis of intracranial neurogenic inflammation (Fig. 2). Hypothalamic CRH may act on the sensory nucleus of the trigeminal nerve, which has been reported to express CRH receptors (Rivest et al., 1995), leading to mast cell stimulating peptides including CRH or urocortin (UCN) to be released from nerve endings; they, in turn, may action mast cells and / or directly on the vasculature (Theoharides et al., in press).

#### 4. Skin inflammation

The important role of mast cells in skin hypersensitivity reactions, a variety of other pathophysiological processes and diseases, as well as wound healing, has been reviewed extensively (Leung et al., 1997; Charlesworth, 1997; Church and Clough, 1999; Noli and Miolo, 2001; Jarvikallio et al.,

2003). Skin mast cells are located close to sensory nerve endings (Wiesner-Menzel et al., 1981) and are known to be activated by neuropeptides (Goetzl et al., 1985, 1990; Foreman, 1987; Church et al., 1989), such as SP (Fewtrell et al., 1982), neurotensin (NT) (Carraway et al., 1982), and pituitary adenylate cyclase activating polypeptide (PACAP) released from human dermal neurons (Odum et al., 1998). In fact, skin mast cells contain SP (Toyoda et al., 2000); cultured mouse and human mast cells also contain and secrete nerve growth factor (NGF) (Xiang and Nilsson, 2000).

Many dermatoses, such as atopic dermatitis and psoriasis, are reportedly triggered or exacerbated by stress (Katsarou-Katsari et al., 1999). It was recently suggested that skin may have its own equivalent of a hypothalamic–pituitary–adrenal (HPA) axis (Slominski and Wortzman, 2000; Slominski et al., 2000) because CRH and its receptors were shown to be present in the skin (Slominski et al., 2001); CRH-2 receptor was further shown to be up-regulated in stress-induced alopecia (Katsarou-Katsari et al., 2001). Acute restraint stress was shown to induce increased skin vascular permeability (Singh et al., 1999b); this effect was inhibited by a CRH receptor antagonist and by a NT-receptor antagonist, while it was absent in mast cell deficient mice (Theoharides et al., 1998a,b; Singh et al., 1999a; Singh et al., 1999b).

CRH (Theoharides et al., 1998a,b) and its structurally related peptide, urocortin (Singh et al., 1999a) also activated skin mast cells and induced mast-cell dependent increase in vascular permeability in rodents. CRH also increased vascular permeability in human skin shown by micro-iontophoresis (Clifton et al., 2002). It was recently shown that acute stress induces local release of CRH in the skin (Lyttinas et al., 2003), further implicating a local stress-induced HPA axis (Slominski et al., 2000). In addition, proteases released from mast cells could act on plasma proteins like albumin to generate histamine releasing peptides (Carraway et al., 1989; Cochrane et al., 2003) that would further propagate mast cell activation and inflammation. Acute stress has also been shown to induce redistribution of leukocytes from the systemic circulation to the skin (Dhabhar and McEwen, 1996) and to exacerbate skin delayed hypersensitivity reactions (Dhabhar and McEwen, 1999) and chronic contact dermatitis in rats, an effect dependent on mast cells and CRH-1 receptors (Kaneko et al., 2003). Acute stress also exacerbated eczema (Graham and Wolf, 1953), and acne vulgaris (Chiu et al., 2003) in humans. Moreover, there was CRH receptor upregulation in affected areas of alopecia areata induced by acute emotional stress (Katsarou-Katsari et al., 2001). The immunoendocrine responses to stress in chronic inflammatory diseases of the skin were reviewed recently (Buske-Kirschbaum and Hellhammer, 2003).

#### 5. Inflammatory arthritis

A number of papers have reported the presence of mast cells in joints (Crisp et al., 1984; Koldewijn et al., 1995;

Woolley, 1995; Tetlow and Woolley, 1995; de Paulis et al., 1996, 1997; Gotis-Graham et al., 1998) and it was justifiably argued that they may be involved in inflammatory arthritis (Woolley, 2003). It was recently reported that mast cells are required for autoimmune arthritis (Lee et al., 2002). At the same time, we showed that acute stress could not induce any increase in vascular permeability in the knee joints of W/W<sup>v</sup> mast cell deficient mice as compared to their +/+ controls (Huang et al., 2002a). We subsequently showed that carrageenin-induced inflammatory arthritis was associated with activated articular mast cells and it also did not develop in mast cell deficient mice (Mattheos et al., 2003). Inflammatory arthritis was also significantly reduced in CRH knockout mice (Mattheos et al., 2003) and in mice treated with the CRH receptor-1 antagonist, Antalarmin (Webster et al., 2002). These findings are even more interesting in view of the fact that mast cells in the joints of rheumatoid arthritis patients express CRH receptors (McEvoy et al., 2001). Moreover, CRH (McEvoy et al., 2001; Lowry et al., 1996) urocortin (Uzuki et al., 2001; Kohno et al., 2001) and CRH receptors are increased in the joints of inflammatory and rheumatoid arthritis patients in whom the symptoms worsen by stress (Thomason et al., 1992; Herrmann et al., 2000). Proteases released from mast cells can, themselves, act as signaling molecules, by stimulating protease-activated receptors on other immune cells, triggering the release of inflammatory molecules. In addition, proteases released from mast cells or other inflammatory cells can generate biologically active peptides like histamine-releasing peptide (HRP) from plasma albumin (Cochrane et al., 1993) and HRP is found in synovial fluids obtained from patients with RA (Cochrane et al., 1989, 2003; Carraway et al., 1987). Moreover, cells obtained from fluid aspirated from joints of patients with arthrosynovitis express RANTES and MCP-1 (Conti et al., 2002), both of which are mast cell chemo-attractants (Conti et al., 1997).

## 6. Cardiopulmonary inflammation

The role of mast cells in asthma is undisputed and has recently been re-emphasized (Cho et al., 2002; Bradding, 2003; Brightling et al., 2003). Moreover, recent reports have indicated that stress can induce asthma exacerbations (Laube et al., 2002; Schmalung et al., 2002; Kilpelainen et al., 2002; Lawrence, 2002; Liu et al., 2002; Bienestock, 2002; Joachim et al., 2003). In fact, one study indicated that maternal stress may be responsible for the cellular response in childhood asthma (von Hertzen, 2002). However, any association with pulmonary mast cells is yet to be made.

On the other hand, increasing evidence implicates acute psychological stress and cardiac mast cells in cardiovascular pathology, especially unstable angina and silent myocardial ischemia (MI). MI occurring without angina on presentation now appears to be a sizable portion of the MI population

(Deanfield et al., 1984; Freeman et al., 1987; Rozanski et al., 1988; Deedwania, 1995). There is growing evidence that cardiac mast cells (Patella et al., 1995) participate in the development of atherosclerosis, coronary inflammation and cardiac ischemia. Mast cells have been identified in coronary arteries during spasm (Forman et al., 1985), and accumulate in the shoulder region of human coronary atheromas, especially in association with plaque rupture (Karttinen et al., 1994; Constantinides, 1995), and MI (Laine et al., 1999). The human mast cell proteolytic enzyme chymase has been shown to be the main cardiac source of converting enzyme generating the coronary constrictor angiotensin II (Jenne and Tschopp, 2003). Cardiac mast cell-derived histamine (Gristwood et al., 1981), can constrict the coronaries (Genovese and Spadaro, 1997); and can sensitize nerve endings (Christian et al., 1989); this action is rendered probable by the recent findings showing adventitial mast cells localized close to nerve endings in atherosclerotic coronary arteries (Laine et al., 2000).

Acute stress induced rat cardiac mast cell activation, documented morphologically, an effect blocked by the “mast cell stabilizer” disodium cromoglycate (cromolyn) and by a NT-receptor antagonist (Pang et al., 1998a). It was later shown that acute stress induced histamine release from mouse heart (Huang et al., 2002a,b), and elevated serum histamine and IL-6 (Huang et al., 2002a,b, 2003). These effects were greater in apolipoprotein E (ApoE) knockout mice that develop atherosclerosis, but were still entirely dependent on mast cells (Huang et al., 2002a,b, 2003). These findings are significant since serum IL-6 elevations in patients with MI were shown to derive primarily from the coronary sinus (Deliargyris et al., 1997), and both histamine (Clejan et al., 2002) and IL-6 (Suzuki et al., 2003) are significant predictive risk factors of coronary events.

## 7. Bladder inflammation

Interstitial cystitis (IC) is a syndrome that appears to occur primarily in women with symptoms of urinary frequency, urgency, nocturia and suprapubic/pelvic pain (Messing and Stamey, 1978; Sant, 1991; Pontari and Hanno, 1995). A recent population estimate in the USA based on the nurses' Health Study (NHS) I and II, that started in 1976 and 1989, respectively, provided a prevalence of about 60 cases/100,000 women (Curhan et al., 1999). The symptoms worsen periodically in 40–50% of premenopausal women and common triggers include psychological or physical stress (Rothrock et al., 2001). Many women with IC have endometriosis and chronic pelvic pain or dyspareunia; moreover, >50% of IC patients have skin or systemic allergic problems, about 40% have irritable bowel syndrome (IBS), and another 30% have fibromyalgia or rheumatoid arthritis (Kozioł et al., 1993; Alagiri et al., 1997). In view of these findings, IC has been considered a neuroinflammatory condition (Theoharides et al., 1998a).

IC patients with nonulcer disease have variable degrees of bladder inflammation on biopsy (Johansson and Fall, 1990). IC patients with bladder inflammation usually present with more pronounced symptoms and increased levels of urine IL-6, but obtain greater relief with bladder hydrodistention (Erickson et al., 1997). Bladder biopsies from IC patients are characterized by some evidence of mucosal damage (Parsons et al., 1991) and an increased number of activated mast cells (Theoharides et al., 1995a; for reviews, see Theoharides and Sant, 1994; Theoharides et al., 2001a), which are positive for IL-6 and/or stem cell factor (SCF) (Pang et al., 1998b; Peeker et al., 2000). Bladder mast cells in IC were located close to increased nerve endings (Christmas et al., 1990; Lundeberg et al., 1993), many of which were SP-positive (Pang et al., 1995a,b); IC bladder biopsies also had higher expression of NK receptors (Marchand et al., 1998). Such mast cells had ultrastructural signs of activation without overt degranulation (Letourneau et al., 1996).

In vivo animal studies showed that the human bladder symptoms could be mimicked since acute stress led to bladder mast cell activation in rodents (Spanos et al., 1977), an action blocked by a NT-receptor antagonist (Alexacos et al., 1999); in contrast, intravesical immune stimulation led to bladder mast cell activation and inflammation through NK-1 receptors; that were not expressed on mast cells (Saban et al., 2002), indicating that different triggers stimulated mast cells through different neuropeptide pathways.

## 8. Gastrointestinal inflammation

The role of mast cells and their interaction with local nerve endings in gastrointestinal pathology (Marshall and Bienenstock, 1994), especially in the intestinal response to bacterial infections (Marshall and Waserman, 1995; Castagliuolo et al., 1994; Pothoulakis et al., 1998); has been reviewed extensively. Mast cells are located close to intestinal neurons (Newson et al., 1983; Skofitsch et al., 1985; Dvorak et al., 1992b; Williams et al., 1995). Even though mucosal mast cells cannot be commonly activated by neuropeptides, it was recently shown that mucosal-like mast cells could make functional associations with neuronal processes through SP (Suzuki et al., 1999) at distinct points of contact (Mori et al., 2002), and could express NK-1 receptors (van der Kleij et al., 2003). Moreover, in rats, NT has been shown to play a significant role in *Clostridium difficile*-induced colonic inflammation and the accompanying activation of mast cells (Castagliuolo et al., 1999).

Neuroimmune interactions have been implicated in food allergies (Frieling et al., 1994), as well as in IBS (O'Sullivan et al., 2000) and in cyclic vomiting syndrome (Fleisher, 1995), both of which can be precipitated by physical or psychological stress (Farthing, 1995; Fleisher, 1997). Recent studies have shown that acute stress by immobilization leads to colonic responses (Williams et al., 1987) associated with gastrointestinal mast cell activation (Castagliuolo et al.,

1996, 1998). This process was dependent on CRH (Castagliuolo et al., 1996). We further showed that CRH can induce intestinal mast cell degranulation directly leading to increased vascular permeability (Theoharides et al., 1999). In fact, mast cells are increased in the intestine of IBS patients (Weston et al., 1993; O'Sullivan et al., 2000), as well as in the intestine and the bladder of a patient with both IBS and IC (Pang et al., 1996b). In both conditions, mast cells were seen in close proximity to local nerve endings (Pang et al., 1996b; Park et al., 2003).

## 9. Mast cells and the HPA axis

CRH can stimulate mast cells, that express CRH receptors (Theoharides et al., 2001) and are localized close to CRH-positive neurons in the median eminence (Theoharides et al., 1995b). Mast cell mediators could, in turn, influence CRH release. For instance, the median eminence of the hypothalamus is rich in mast cells (Pollard et al., 1976; Panula et al., 1984) and contains most of the histamine in the brain (Yamatodani et al., 1982). Histamine had been considered a major regulator in the hypothalamus (Roberts and Calcutt, 1983), and was later shown to increase CRH mRNA expression in the hypothalamus (Kjaer et al., 1998). In fact, hypothalamic mast cell activation led to stimulation of the HPA axis (Bugajski et al., 1995a,b; Gadek-Michalska et al., 1991; Matsumoto et al., 2001). Moreover, human mast cells were recently shown to synthesize and secrete large amounts of both CRH and urocortin (Kempuraj et al., in press), implying that they are both a source and a target of stress-related neuropeptides. Moreover, mast cells are also found in the human pituitary (Cromlish et al., 1987) and can be stimulated by pituitary products such as luteinizing hormone releasing hormone (Sundaram et al., 1988) or PACAP (Seebeck et al., 1998). In addition, NT, which is known to activate mast cells (Carraway et al., 1982) is present in the pituitary and median eminence (Bello et al., 1999). NT has also been shown to participate in stress-induced activation of mast cells (Alexacos et al., 1999; Pang et al., 1998a) and in stress-related HPA activity (Rowe et al., 1997). Inhibition of mast cell activation, therefore, could be of critical importance in treating inflammatory and autoimmune disorders. Certain dietary supplements (Theoharides, 2003) have recently been shown to be effective in this regard (Theoharides, 2003) because they combine chondroitin sulfate (Theoharides et al., 2000) and quercetin (Middleton et al., 2000; Theoharides et al., 2001b) both of which have mast cell inhibitory and anti-inflammatory actions.

## 10. Conclusion

In summary, the mast cell has emerged as a unique immune cell that could be activated by many non-immune

processes, including acute stress (Theoharides, 2002), and could participate in a variety of inflammatory diseases in the nervous system, skin, joints, as well as cardiopulmonary, intestinal and urinary systems (Theoharides, 1996).

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## References

- Ackerman, K.D., Heyman, R., Rabin, B.S., Anderson, B.P., Houck, P.R., Frank, E., Baum, A., 2002. Stressful life events precede exacerbations of multiple sclerosis. *Psychosom. Med.* 64, 916–920.
- Alagiri, M., Chottiner, S., Ratner, V., Slade, D., Hanno, P.M., 1997. Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. *Urology* 49 (Suppl. 5A), 52–57.
- Alexacos, N., Pang, X., Boucher, W., Cochrane, D.E., Sant, G.R., Theoharides, T.C., 1999. Neurotensin mediates rat bladder mast cell degranulation triggered by acute psychological stress. *Urology* 53, 1035–1040.
- Bello, A.R., Hernandez, G., Gonzalez, M., Reyes, R., Negrin, I., Marrero, A., Sanchez-Criado, J.E., Tramu, G., Alonso, R., 1999. Immunoreactive neurotensin in gonadotrophs and thyrotrophs is regulated by sex steroid hormones in the female rat. *J. Neuroendocrinol.* 11, 785–794.
- Belova, I., Jonsson, G., 1982. Blood–brain barrier permeability and immobilization stress. *Acta Physiol. Scand.* 116, 21–29.
- Benoist, C., Mathis, D., 2002. Mast cells in autoimmune disease. *Nature* 420, 875–878.
- Benyon, R., Robinson, C., Church, M.K., 1989. Differential release of histamine and eicosanoids from human skin mast cells activated by IgE-dependent and non-immunological stimuli. *Br. J. Pharmacol.* 97, 898–904.
- Bienenstock, J., 2002. Stress and asthma: the plot thickens. *Am. J. Respir. Crit. Care Med.* 165, 1034–1035.
- Bradding, P., 2003. The role of the mast cell in asthma: a reassessment. *Curr. Opin. Allergy Clin. Immunol.* 3, 45–50.
- Brenner, T., Soffer, D., Shalit, M., Levi-Schaffer, F., 1994. Mast cells in experimental allergic encephalomyelitis: characterization, distribution in the CNS and in vitro activation by myelin basic protein and neuropeptides. *J. Neurol. Sci.* 122, 210–213.
- Brightling, C.E., Bradding, P., Pavord, I.D., Wardlaw, A.J., 2003. New insights into the role of the mast cell in asthma. *Clin. Exp. Allergy* 33, 550–556.
- Brown, M., Tanzola, M., Robbie-Ryan, M., 2002. Mechanisms underlying mast cell influence on EAE disease course. *Mol. Immunol.* 38, 1373–1378.
- Bugajski, A.J., Chlap, Z., Bugajski, J., Borycz, J., 1995a. Effect of compound 48/80 on mast cells and biogenic amine levels in brain structures and on corticosterone secretion. *J. Physiol. Pharmacol.* 46, 513–522.
- Bugajski, A.J., Chlap, Z., Gadek-Michalska, A., Borycz, J., Bugajski, J., 1995b. Degranulation and decrease in histamine levels of thalamic mast cells coincides with corticosterone secretion induced by compound 48/80. *Inflamm. Res.* 44 (Suppl. 1), S50–S51.
- Buske-Kirschbaum, A., Hellhammer, D.H., 2003. Endocrine and immune responses to stress in chronic inflammatory skin disorders. *Ann. N.Y. Acad. Sci.* 992, 231–240.
- Carraway, R., Cochrane, D.E., Lansman, J.B., Leeman, S.E., Paterson, B.M., Welch, H.J., 1982. Neurotensin stimulates exocytotic histamine secretion from rat mast cells and elevates plasma histamine levels. *J. Physiol.* 323, 403–414.
- Carraway, R.E., Mitra, S.P., Cochrane, D.E., 1987. Structure of a biologically active neurotensin-related peptide obtained from pepsin-treated albumin(s). *J. Biol. Chem.* 262, 5968–5973.
- Carraway, R.E., Cochrane, D.E., Boucher, W., Mitra, S.P., 1989. Structures of histamine-releasing peptides formed by the action of acid proteases on mammalian albumin(s). *J. Immunol.* 143, 1680–1684.
- Castagliuolo, I., LaMont, J.T., Letourneau, R., Kelly, C., O’Keane, J.C., Jaffer, A., Theoharides, T.C., Pothoulakis, C., 1994. Neuronal involvement in the intestinal effects of *Clostridium difficile* toxin A and *vibrio cholera* enterotoxin in rat ileum. *Gastroenterology* 107, 657–665.
- Castagliuolo, I., LaMont, J.T., Qiu, B., Fleming, S.M., Bhaskar, K.R., Nikulasson, S.T., Kornetsky, C., Pothoulakis, C., 1996. Acute stress causes mucin release from rat colon: role of corticotropin releasing factor and mast cells. *Am. J. Physiol.* 271, 884–892.
- Castagliuolo, I., Wershil, B.K., Karalis, K., Pasha, A., Nikulasson, S.T., Pothoulakis, C., 1998. Colonic mucin release in response to immobilization stress is mast cell dependent. *Am. J. Physiol.* 274, 1000–1094.
- Castagliuolo, I., Wang, C.C., Valenich, L., Pasha, A., Nikulassin, S., Carraway, R.E., 1999. Neurotensin is a proinflammatory neuropeptide in colonic inflammation. *J. Clin. Invest.* 103, 843–849.
- Chandler, N., Jacobson, S., Connolly, R., Esposito, P., Theoharides, T.C., 2002. Acute stress shortens the time of onset of experimental allergic encephalomyelitis (EAE) in SJL/J mice. *Brain Behav. Immun.* 16, 757–763.
- Charlesworth, E.N., 1997. The role of basophils and mast cells in acute and late reactions in the skin. *Allergy* 52 (34 Suppl.), 31–43.
- Chiu, A., Chon, S.Y., Kimball, A.B., 2003. The response of skin disease to stress: changes in the severity of acne vulgaris as affected by examination stress. *Arch. Dermatol.* 139, 897–900.
- Cho, S.H., Anderson, A.J., Oh, C.K., 2002. Importance of mast cells in the pathophysiology of asthma. *Clin. Rev. Allergy Immunol.* 22, 161–174.
- Christian, E.P., Udem, B.J., Weinreich, D., 1989. Endogenous histamine excites neurones in the guinea-pig superior cervical ganglion in vitro. *J. Physiol.* 409, 297–312.
- Christmas, T.J., Rode, J., Chapple, C.R., Milroy, E.J., Turner-Warwick, R.T., 1990. Nerve fibre proliferation in interstitial cystitis. *Virchows Arch. A* 416, 447–451.
- Chrousos, G.P., 1995. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. *N. Engl. J. Med.* 332, 1351–1362.
- Church, M.K., Clough, G.F., 1999. Human skin mast cells: in vitro and in vivo studies. *Ann. Allergy, Asthma, and Immun.* 83, 471–475.
- Church, M.K., Lowman, M.A., Rees, P.H., Benyon, R.C., 1989. Mast cells, neuropeptides and inflammation. *Agents Actions* 27, 8–16.
- Clejan, S., Japa, S., Clemetson, C., Hasabnis, S.S., David, O., Talamo, J.V., 2002. Blood histamine is associated with coronary artery disease, cardiac events and severity of inflammation and atherosclerosis. *J. Cell. Mol. Med.* 6, 502–583.
- Clifton, V.L., Crompton, R., Smith, R., Wright, I.M., 2002. Microvascular effects of CRH in human skin vary in relation to gender. *J. Clin. Endocrinol. Metab.* 87, 267–270.
- Cochrane, D.E., Boucher, W., Carraway, R.E., 1989. Generation of histamine-releasing activity from serum albumin by medium derived from stimulated neutrophils of rat. *Br. J. Pharmacol.* 97, 524–532.
- Cochrane, D.E., Carraway, R.E., Feldberg, R.S., Boucher, W., Gelfand, J.M., 1993. Stimulated rat mast cells generate histamine-releasing peptide from albumin. *Peptides* 14, 117–123.
- Cochrane, D.E., Carraway, R.E., Miller, L.A., Feldberg, R.S., Bernheim,

- H., 2003. Histamine releasing peptide (HRP) has proinflammatory effects and is present at sites of inflammation. *Biochem. Pharmacol.* 66, 331–342.
- Constantinides, P., 1995. Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. *Circulation* 92, 1083–1088.
- Conti, P., Pang, X., Boucher, W., Letourneau, R., Reale, M., Barbacane, R.C., Thibault, J., Theoharides, T.C., 1997. Impact of RANTES and MCP-1 chemokines on *in vivo* basophilic mast cell recruitment in rat skin injection model and their role in modifying the protein and mRNA levels for histidine decarboxylase. *Blood* 89, 4120–4127.
- Conti, P., Reale, M., Barbacane, R.C., Letourneau, R., Theoharides, T.C., 1998. Intramuscular injection of hrRANTES causes mast cell recruitment and increased transcription of histidine decarboxylase: lack of effects in genetically mast cell-deficient W/W<sup>v</sup> mice. *FASEB J.* 12, 1693–1700.
- Conti, P., Reale, M., Barbacane, R.C., Castellani, M.L., Orso, C., 2002. Differential production of RANTES and MCP-1 in synovial fluid from the inflamed human knee. *Immunol. Lett.* 80, 105–111.
- Crisp, A.J., Champan, C.M., Kirkham, S.E., Schiller, A.L., Keane, S.M., 1984. Articular mastocytosis in rheumatoid arthritis. *Arthritis Rheum.* 27, 845–851.
- Cromlish, J.A., Seidah, N.G., Marcinkiewicz, M., Hamelin, J., Johnson, D.A., Chretien, M., 1987. Human pituitary tryptase: molecular forms, NH<sub>2</sub>-terminal sequence, immunocytochemical localization, and specificity with prohormone and fluorogenic substrates. *J. Biol. Chem.* 262, 1363–1373.
- Curhan, G.C., Speizer, F.E., Hunter, D.J., Curhan, S.G., Stampfer, M.J., 1999. Epidemiology of interstitial cystitis: a population based study. *J. Urol.* 161, 549–552.
- de Paulis, A., Marino, I., Ciccarelli, A., de Crescenzo, G., Concardi, M., Verga, L., Arbustini, E., Marone, G., 1996. Human synovial mast cells: I. Ultrastructural *in situ* and *in vitro* immunologic characterization. *Arthritis Rheum.* 39, 1222–1233.
- de Paulis, A., Ciccarelli, A., Marinò, I., de Crescenzo, G., Marinò, D., Marone, G., 1997. Human synovial mast cells: II. Heterogeneity of the pharmacologic effects of antiinflammatory and immunosuppressive drugs. *Arthritis Rheum.* 40, 469–478.
- De Vreis, H.E., Kuiper, J., de Boer, A.G., Van Berkel, T.J.C., Breimer, D.D., 1997. The blood–brain barrier in neuroinflammatory diseases. *Pharmacol. Rev.* 49, 143–155.
- Deanfield, J.E., Shea, M., Kensett, M., Horlock, P., Wilson, R.A., de Landsheare, C.M., Selwyn, A.P., 1984. Silent myocardial ischaemic due to mental stress. *Lancet* 2 (8410), 1001–1005.
- Deedwania, P.C., 1995. Mental stress, pain perception and risk of silent ischemia. *J. Am. J. Cardiol.* 25 (7), 1504–1506.
- Deliargyris, E.N., Raymond, R.J., Theoharides, T.C., Boucher, W.S., Tate, D.A., Dehmer, G.J., 2000. Sites of interleukin-6 release in patients with acute coronary syndromes and in patients with congestive heart failure. *Am. J. Cardiol.* 86, 913–918.
- Dhabhar, F., McEwen, B.S., 1996. Stress-induced enhancement of antigen-specific cell-mediated immunity. *J. Immunol.* 156, 2608–2615.
- Dhabhar, F.S., McEwen, B.S., 1999. Enhancing versus suppressive effects of stress hormones on skin immune function. *Proc. Natl. Acad. Sci. U. S. A.* 96, 1059–1064.
- Dietsch, G.N., Hinrichs, D.J., 1991. Mast cell proteases liberate encephalogenic fragments from intact myelin. *Cell. Immunol.* 135, 541–548.
- Dimitriadou, V., Aubineau, P., Taxi, J., Seylaz, J., 1987. Ultrastructural evidence for a functional unit between nerve fibers and type II cerebral mast cells in the cerebral vascular wall. *Neuroscience* 22, 621–630.
- Dimitriadou, V., Lambrecht-Hall, M., Reichler, J., Theoharides, T.C., 1990. Histochemical and ultrastructural characteristics of rat brain perivascular mast cells stimulated with compound 48/80 and carbachol. *Neuroscience* 39, 209–224.
- Dimitriadou, V., Buzzi, M.G., Moskowitz, M.A., Theoharides, T.C., 1991. Trigeminal sensory fiber stimulation induces morphologic changes reflecting secretion in rat dura mast cells. *Neuroscience* 44, 97–112.
- Dimitriadou, V., Buzzi, M.G., Theoharides, T.C., Moskowitz, M.A., 1992. Ultrastructural evidence for neurogenically mediated changes in blood vessels of the rat dura mater and tongue following antidromic trigeminal stimulation. *Neuroscience* 48, 187–203.
- Dimitriadou, V., Pang, X., Theoharides, T.C., 2000. Hydroxyzine inhibits experimental allergic encephalomyelitis (EAE) and associated brain mast cell activation. *Int. J. Immunopharmacol.* 22, 673–684.
- Dines, K.C., Powell, H.C., 1997. Mast cell interactions with the nervous system: relationship to mechanisms of disease. *J. Neuropathol. Exp. Neurol.* 56, 627–640.
- Dvorak, A.M., McLeod, R.S., Onderdonk, A., Monahan-Earley, R.A., Cullen, J.B., Antonioli, D.A., Morgan, E., Blair, J.E., Estrella, P., Cisneros, R.L., Silen, W., Cohen, Z., 1992a. Ultrastructural evidence for piecemeal and anaphylactic degranulation of human gut mucosal mast cells *in vivo*. *Int. Arch. Allergy Immunol.* 99, 74–83.
- Dvorak, A.M., McLeod, R.S., Onderdonk, A.B., Monahan-Earley, R.A., Cullen, J.B., Antonioli, D.A., Morgan, E., Blair, J.E., Estrella, P., Cisneros, R.L., 1992b. Human gut mucosal mast cells: ultrastructural observations and anatomic variation in mast cell-nerve associations *in vivo*. *Int. Arch. Allergy Immunol.* 98, 158–168.
- Erickson, D.R., Belchis, D.A., Dabbs, D.J., 1997. Inflammatory cell types and clinical features of interstitial cystitis. *J. Urol.* 158, 790–793.
- Espósito, P., Gheorghe, D., Kandere, K., Pang, X., Conally, R., Jacobson, S., Theoharides, T.C., 2001. Acute stress increases permeability of the blood–brain-barrier through activation of brain mast cells. *Brain Res.* 888, 117–127.
- Espósito, P., Chandler, N., Kandere-Grzybowska, K., Basu, S., Jacobson, S., Connolly, R., Tutor, D., Theoharides, T.C., 2002. Corticotropin-releasing hormone (CRH) and brain mast cells regulate blood–brain-barrier permeability induced by acute stress. *J. Pharmacol. Exp. Ther.* 303, 1061–1066.
- Espósito, P., Basu, S., Letourneau, R., Jacobson, S., Theoharides, T.C., 2003. Corticotropin-releasing factor (CRF) can directly affect brain microvessel endothelial cells. *Brain Res.* 968, 192–198.
- Farthing, M.J.G., 1995. Irritable bowel, irritable body, or irritable brain? *Br. Med. J.* 310, 171–175.
- Fewtrell, C.M.S., Foreman, J.C., Jordan, C.C., Oehme, P., Renner, H., Stewart, M., 1982. The effects of substance P on histamine and 5-hydroxytryptamine release in the rat. *J. Physiol.* 330, 393–411.
- Fleisher, D.R., 1995. The cyclic vomiting syndrome described. *J. Pediatr. Gastroenterol. Nutr.* 21 (Suppl. 1), S1–S5.
- Fleisher, D.R., 1997. Cyclic vomiting syndrome: a paroxysmal disorder of brain–gut interaction. *J. Pediatr. Gastroenterol. Nutr.* 25, S13–S15.
- Foreman, J.C., 1987. Neuropeptides and the pathogenesis of allergy. *Allergy* 42, 1–11.
- Forman, M.B., Oates, J.A., Robertson, D., Robertson, R.M., Roberts II, L.J., Virmani, R., 1985. Increased adventitial mast cells in a patient with coronary spasm. *N. Engl. J. Med.* 313, 1138–1141.
- Freeman, L.J., Nixon, P.G.F., Sallabank, P., Reaveley, D., 1987. Psychological stress and silent myocardial ischemia. *Am. Heart J.* 114, 477–482.
- Frieling, T., Cooke, H.J., Wood, J.D., 1994. Neuroimmune communication in the submucous plexus of guinea pig colon after sensitization to milk antigen. *Am. J. Physiol.: Gastrointest. Liver Physiol.* 267, 1087–1093.
- Gadek-Michalska, A., Chlap, Z., Turon, M., Bugajski, J., Fogel, W.A., 1991. The intracerebroventricularly administered mast cells degranulator compound 48/80 increases the pituitary–adrenocortical activity in rats. *Agents Actions* 32, 203–208.
- Gagari, E., Tsai, M., Lantz, C.S., Fox, L.G., Galli, S.J., 1997. Differential release of mast cell interleukin-6 via c-kit. *Blood* 89, 2654–2663.
- Galli, S.J., 1993. New concepts about the mast cell. *N. Engl. J. Med.* 328, 257–265.
- Galli, S.J., Wedemeyer, J., Tsai, M., 2002. Analyzing the roles of mast cells and basophils in host defense and other biological responses. *Int. J. Hematol.* 75, 363–369.
- Genovese, A., Spadaro, G., 1997. Highlights in cardiovascular effects of histamine and H1-receptor antagonists. *Allergy* 52 (Suppl. 34), 67–78.



- Goetzl, E.J., Chernov, T., Renold, F., Payan, D.G., 1985. Neuropeptide regulation of the expression of immediate hypersensitivity. *J. Immunol.* 135, 802s–805s.
- Goetzl, E.J., Cheng, P.P.J., Hassner, A., Adelman, D.C., Frick, O.L., Speedharan, S.P., 1990. Neuropeptides, mast cells and allergy: novel mechanisms and therapeutic possibilities. *Clin. Exp. Allergy* 20, 3–7.
- Goodin, D.S., Ebers, G.C., Johnson, K.P., Rodriguez, M., Sibley, W.A., Wolinsky, J.S., 1999. The relationship of MS to physical trauma and psychological stress. *Neurology* 52, 1737–1745.
- Gotis-Graham, I., Smith, M.D., Parker, A., McNeil, H.P., 1998. Synovial mast cell responses during clinical improvement in early rheumatoid arthritis. *Ann. Rheum. Dis.* 57, 664–671.
- Graham, D.T., Wolf, S., 1953. The relation of eczema to attitude and to vascular reactions of the human skin. *J. Lab. Clin. Med.* 42, 238–254.
- Gristwood, R.W., Lincoln, J.C., Owen, D.A., Smith, I.R., 1981. Histamine release from human right atrium. *Br. J. Pharmacol.* 74, 7–9.
- Gurish, M.F., Austen, K.F., 2001. The diverse roles of mast cells. *J. Exp. Med.* 194, 1–6.
- Habib, K.E., Gold, P.W., Chrousos, G.P., 2001. Neuroendocrinology of stress. *Endocrinol. Metab. Clin. N. Am.* 30, 695–728.
- Herrmann, M., Scholmerich, J., Straub, R.H., 2000. Stress and rheumatic diseases. *Rheum. Dis. Clin. North Am.* 26, 737–763.
- Hojo, H., Sun, R., Ono, Y., Shishido, T., Obara, E., Yamazoe, Y., Hashimoto, Y., 1996. Differential production of interleukin-6 and its close relation to liver metastasis in clones from murine P815 mastocytoma. *Cancer Lett.* 108, 55–59.
- Huang, M., Berry, J., Kandere, K., Lytinas, M., Karalis, K., Theoharides, T.C., 2002a. Mast cell deficient W/W(v) mice lack stress-induced increase in serum IL-6 levels, as well as in peripheral CRH and vascular permeability, a model of rheumatoid arthritis. *Int. J. Immunopathol. Pharmacol.* 15, 249–254.
- Huang, M., Pang, X., Letourneau, L., Boucher, W., Theoharides, T.C., 2002b. Acute stress induces cardiac mast cell activation and histamine release, effects that are increased in apolipoprotein E knockout mice. *Cardiovasc. Res.* 55, 150–160.
- Huang, M., Pang, X., Karalis, K., Theoharides, T.C., 2003. Stress-induced interleukin-6 release in mice is mast cell-dependent and more pronounced in apolipoprotein E knockout mice. *Cardiovasc. Res.* 59, 241–249.
- Ibrahim, M.Z.M., Reder, A.T., Lawand, R., Takash, W., Sallouh-Khatib, S., 1996. The mast cells of the multiple sclerosis brain. *J. Neuroimmunol.* 70, 131–138.
- Jarvikallio, A., Harvima, I.T., Naukkarinen, A., 2003. Mast cells, nerves and neuropeptides in atopic dermatitis and nummular eczema. *Arch. Dermatol. Res.* 295, 2–7.
- Jenne, D.E., Tschopp, J., 1991. Angiotensin II-forming heart chymase is a mast-cell-specific enzyme. *Biochem. J.* 276, 567.
- Joachim, R.A., Quarcoo, D., Arck, P.C., Herz, U., Renz, H., Klapp, B.F., 2003. Stress enhances airway reactivity and airway inflammation in an animal model of allergic bronchial asthma. *Psychosom. Med.* 65, 811–815.
- Johansson, S., Fall, M., 1990. Clinical features and spectrum of light microscopic changes in interstitial cystitis. *J. Urol.* 143, 1118–1124.
- Johnson, D., Seeldrayers, P.A., Weiner, H.L., 1988. The role of mast cells in demyelination: 1. Myelin proteins are degraded by mast cell proteases and myelin basic protein and P<sub>2</sub> can stimulate mast cell degranulation. *Brain Res.* 444, 195–198.
- Kaartinen, M., Penttilä, A., Kovanen, P.T., 1994. Accumulation of activated mast cells in the shoulder region of human coronary atheroma, the predilection site of atheromatous rupture. *Circulation* 90, 1669–1678.
- Kandere-Grzybowska, K., Georghe, D., Esposito, P., Huang, M., Gerard, N.P., Theoharides, T.C., 2003a. Stress-induced dura vascular permeability does not develop in mast cell deficient and neurokinin-1 receptor knockout mice. *Brain Res.* 980, 213–220.
- Kandere-Grzybowska, K., Letourneau, R., Donelan, J., Kempuraj, D., Theoharides, T.C., 2003b. Interleukin-1-induced vesicular secretion of interleukin-6 without degranulation from human mast cells. *J. Immunol.* 171, 4830–4836.
- Kaneko, K., Kawana, K.K., Arai, K., Shibasaki, T., 2003. Corticotropin-releasing factor receptor type 1 is involved in the stress-induced exacerbation of chronic contact dermatitis in rats. *Exp. Dermatol.* 12, 47–52.
- Karalis, K., Sano, H., Redwine, J., Listwak, S., Wilder, R.L., Chrousos, G.P., 1991. Autocrine or paracrine inflammatory actions of corticotropin-releasing hormone in vivo. *Science* 254, 421–423.
- Katsarou-Katsari, A., Filippou, A., Theoharides, T.C., 1999. Effect of stress and other psychological factors on the pathophysiology and treatment of dermatoses. *Int. J. Immunopathol. Pharmacol.* 12, 7–11.
- Katsarou-Katsari, A., Singh, L.K., Theoharides, T.C., 2001. Alopecia areata and affected skin CRH receptor upregulation induced by acute emotional stress. *Dermatology* 203, 157–161.
- Kempuraj, D., Papadopoulou, N., Lytinas, M., Kandere-Grzybowska, K., Huang, M., Madhappan, B., Christodoulou, S., Athanassiou, A., Theoharides, T.C., 2003. Human mast cells synthesize and secrete corticotropin-releasing hormone (CRH) which triggers them to secrete IL-6. *Endocrinology* (in press).
- Kilpelainen, M., Koskenvuo, M., Helenius, H., Terho, E.O., 2002. Stressful life events promote the manifestation of asthma and atopic diseases. *Clin. Exp. Allergy* 32, 256–263.
- Kjaer, A., Larsen, P.J., Knigge, U., Jorgensen, H., Warberg, J., 1998. Neuronal histamine and expression of corticotropin-releasing hormone, vasopressin and oxytocin in the hypothalamus: relative importance of H<sub>1</sub> and H<sub>2</sub> receptors. *Eur. J. Endocrinol.* 139, 238–243.
- Kobayashi, H., Ishizuka, T., Okayama, Y., 2000. Human mast cells and basophils as sources of cytokines. *Clin. Exp. Allergy* 30 (9), 1205–1212.
- Kohno, M., Kawahito, Y., Tsubouchi, Y., Hashiramoto, A., Yamada, R., Inoue, K.I., Kusaka, Y., Kubo, T., Elenkov, I.J., Chrousos, G.P., Kondo, M., Sano, H., 2001. Urocortin expression in synovium of patients with rheumatoid arthritis and osteoarthritis: relation to inflammatory activity. *J. Clin. Endocrinol. Metab.* 86, 4344–4352.
- Koldewijn, E.L., Hommes, O.R., Lemmens, W.A.J.G., Debruyne, F.M.J., Van Kerrebroeck, P.E.V., 1995. Relationship between lower urinary tract abnormalities and disease-related parameters in multiple sclerosis. *J. Urol.* 154, 169–173.
- Kops, S.K., Van Loveren, H., Rosenstein, R.W., Ptak, W., Askenase, P.W., 1984. Mast cell activation and vascular alterations in immediate hypersensitivity-like reactions induced by a T cell derived antigen-binding factor. *Lab. Invest.* 50, 421–434.
- Kops, S.K., Theoharides, T.C., Cronin, C.T., Kashgarian, M.G., Askenase, P.W., 1990. Ultrastructural characteristics of rat peritoneal mast cells undergoing differential release of serotonin without histamine and without degranulation. *Cell Tissue Res.* 262, 415–424.
- Kozioł, J.A., Clark, D.C., Gittes, R.F., Tan, E.M., 1993. The natural history of interstitial cystitis: a survey of 374 patients. *J. Urol.* 149, 465–469.
- Krüger, P.G., Bo, L., Myhr, K.M., Karlsen, A.E., Taule, A., Nyland, H.I., Mork, S., 1990. Mast cells and multiple sclerosis: a light and electron microscopic study of mast cells in multiple sclerosis emphasizing staining procedures. *Acta Neurol. Scand.* 81, 31–36.
- Kwon, E.E., Prineas, J.W., 1994. Blood–brain barrier abnormalities in longstanding multiple sclerosis lesions. An immunohistochemical study. *J. Neuropathol. Exp. Neurol.* 53, 625–636.
- Laine, P., Kaartinen, M., Penttilä, A., Panula, P., Paavonen, T., Kovanen, P.T., 1999. Association between myocardial infarction and the mast cells in the adventitia of the infarct-related coronary artery. *Circulation* 99, 361–369.
- Laine, P., Naukkarinen, A., Heikkilä, L., Penttilä, A., Kovanen, P.T., 2000. Adventitial mast cells connect with sensory nerve fibers in atherosclerotic coronary arteries. *Circulation* 101, 1665–1669.
- Laube, B.L., Curbow, B.A., Costello, R.W., Fitzgerald, S.T., 2002. A pilot study examining the relationship between stress and serum cortisol concentrations in women with asthma. *Respir. Med.* 96, 823–828.
- Lawrence, D.A., 2002. Psychologic stress and asthma: neuropeptide involvement. *Environ. Health Perspect.* 110, A230–A231.

- Leal-Berumen, I., Conlon, P., Marshall, J.S., 1994. IL-6 production by rat peritoneal mast cells is not necessarily preceded by histamine release and can be induced by bacterial lipopolysaccharide. *J. Immunol.* 152, 5468–5476.
- Lee, D.M., Friend, D.S., Gurish, M.F., Benoist, C., Mathis, D., Brenner, M.B., 2002. Mast cells: a cellular link between autoantibodies and inflammatory arthritis. *Science* 297, 1689–1692.
- Letourneau, R., Pang, X., Sant, G.R., Theoharides, T.C., 1996. Intragranular activation of bladder mast cells and their association with nerve processes in interstitial cystitis. *Br. J. Urol.* 77, 41–54.
- Letourneau, R., Rozniecki, J.J., Dimitriadou, V., Theoharides, T.C., 2003. Ultrastructural evidence of brain mast cell activation without degranulation in monkey EAE. *J. Neuroimmunol.* (in press).
- Leung, D.Y., Diaz, L.A., DeLeo, V., Soter, N.A., 1997. Allergic and immunologic skin disorders. *JAMA* 278, 1914–1923.
- Levi-Schaffer, F., Shalit, M., 1989. Differential release of histamine and prostaglandin D<sub>2</sub> in rat peritoneal mast cells activated with peptides. *Int. Arch. Allergy Appl. Immunol.* 90, 352–357.
- Liu, L.Y., Coe, C.L., Swenson, C.A., Kelly, E.A., Kita, H., Busse, W.W., 2002. School examinations enhance airway inflammation to antigen challenge. *Am. J. Respir. Crit. Care Med.* 15 (165), 1062–1067.
- Lock, C., Hermans, G., Pedotti, R., Brendolan, A., Schadt, E., Garren, H., Langer-Gould, A., Strober, S., Cannella, B., Allard, J., Klonowski, P., Austin, A., Lad, N., Kaminski, N., Galli, S.J., Oksenberg, J.R., Raine, C.S., Heller, R., Steinman, L., 2002. Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nat. Med.* 8, 500–508.
- Lowry, P.J., Woods, R.J., Baigent, S., 1996. Corticotropin releasing factor and its binding protein. *Pharmacol. Biochem. Behav.* 54, 305–308.
- Lundeberg, T., Liedberg, H., Nordling, L., Theodorsson, E., Owzarski, A., Ekman, P., 1993. Interstitial cystitis: correlation with nerve fibres, mast cells and histamine. *Br. J. Urol.* 71, 427–429.
- Lytinas, M., Kempuraj, D., Huang, M., Boucher, W., Esposito, P., Theoharides, T.C., 2003. Acute stress results in skin corticotropin-releasing hormone secretion, mast cell activation and vascular permeability, an effect mimicked by intradermal corticotropin-releasing hormone and inhibited by histamine-1 receptor antagonists. *Int. Arch. Allergy Immunol.* 130, 224–231.
- Malaviya, R., Abraham, S.N., 2001. Mast cell modulation of immune responses to bacteria. *Immunol. Rev.* 179, 16–24.
- Marchand, J.E., Sant, G.R., Kream, R.M., 1998. Increased expression of substance P receptor-encoding mRNA in bladder biopsies from patients with interstitial cystitis. *Br. J. Urol.* 81, 224–228.
- Marone, G., Galli, S.J., Kitamura, Y., 2002. Probing the roles of mast cells and basophils in natural and acquired immunity. *Trends Immunol.* 23, 425–427.
- Marquardt, D.L., Alongi, J.L., Walker, L.L., 1996. The phosphatidylinositol 3-kinase inhibitor wortmannin blocks mast cell exocytosis but not IL-6 production. *J. Immunol.* 156, 1942–1945.
- Marshall, J.S., Bienenstock, J., 1994. The role of mast cells in inflammatory reactions of the airways, skin and intestine. *Curr. Opin. Immunol.* 6, 853–859.
- Marshall, J.S., Wasserman, S., 1995. Mast cells and the nerves—potential interactions in the context of chronic disease. *Clin. Exp. Allergy* 25, 102–110.
- Matsumoto, I., Inoue, Y., Shimada, T., Aikawa, T., 2001. Brain mast cells act as an immune gate to the hypothalamic–pituitary–adrenal axis in dogs. *J. Exp. Med.* 194, 71–78.
- Mattheos, S., Christodoulou, S., Kempuraj, D., Kempuraj, B., Karalis, K., Theoharides, T.C., 2003. Mast cells and corticotropin-releasing hormone (CRH) are required for experimental inflammatory arthritis. *FASEB J.* 17, C44.
- McEvoy, A.N., Bresnihan, B., FitzGerald, O., Murphy, E.P., 2001. Corticotropin-releasing hormone signaling in synovial tissue from patients with early inflammatory arthritis is mediated by the type 1 $\alpha$  corticotropin-releasing hormone receptor. *Arthritis Rheum.* 44, 1761–1767.
- Mei-Tal, V., Meyerowitz, S., Engel, G.L., 1970. The role of psychological process in a somatic disorder: multiple sclerosis: 1. The emotional setting of illness onset and exacerbation. *Psychosom. Med.* 32, 67–86.
- Messing, E.M., Stamey, T.A., 1978. Interstitial cystitis: early diagnosis, pathology and treatment. *Urology* 12, 381–392.
- Middleton Jr., E., Kandaswami, C., Theoharides, T.C. 2000. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. *Pharmacol. Res.* 52, 673–751.
- Mohr, D.C., Goodkin, D.E., Bacchetti, P., Boudewyn, A.C., Huang, L., Marrietta, P., Cheuk, W., Dee, B., 2000. Psychological stress and the subsequent appearance of new brain MRI lesions in MS. *Neurology* 55, 55–61.
- Mori, N., Suzuki, R., Furuno, T., McKay, D.M., Wada, M., Teshima, R., Bienenstock, J., Nakanishi, M., 2002. Nerve-mast cell (RBL) interaction: RBL membrane ruffling occurs at the contact site with an activated neurite. *Am. J. Physiol., Cell Physiol.* 283, C1738–C1744.
- Newson, B., Dahlström, A., Enerbäck, L., Ahlman, H., 1983. Suggestive evidence for a direct innervation of mucosal mast cells. *Neuroscience* 10, 565–570.
- Noli, C., Miolo, A., 2001. The mast cell in wound healing. *Vet. Dermatol.* 12, 303–313.
- Odum, L., Petersen, L.J., Skov, P.S., Ebskov, L.B., 1998. Pituitary adenylylate cyclase activating polypeptide (PACAP) is localized in human dermal neurons and causes histamine release from skin mast cells. *Inflamm. Res.* 47, 488–492.
- Okayama, Y., Benyon, R.C., Rees, P.H., Lowman, M.A., Hillier, K., Church, M.K., 1992. Inhibition profiles of sodium cromoglycate and nedocromil sodium on mediator release from mast cells of human skin, lung, tonsil, adenoid and intestine. *Clin. Exp. Allergy* 22, 401–409.
- Olness, K., Hall, H., Rozniecki, J.J., Schmidt, W., Theoharides, T.C., 1999. Mast cell activation in child migraine patients before and after training in self-regulation. *Headache* 39, 101–107.
- Olsson, Y., 1974. Mast cells in plaques of multiple sclerosis. *Acta Neurol. Scand.* 50, 611–618.
- O'Sullivan, M., Clayton, N., Breslin, N.P., Harman, I., Bountra, C., McLaren, A., O'Morain, C.A., 2000. Increased mast cells in the irritable bowel syndrome. *Neurogastroenterol. Motil.* 12, 449–457.
- Pang, X., Cotreau-Bibbo, M.M., Sant, G.R., Theoharides, T.C., 1995a. Bladder mast cell expression of high affinity oestrogen receptors in patients with interstitial cystitis. *Br. J. Urol.* 75, 154–161.
- Pang, X., Marchand, J., Sant, G.R., Kream, R.M., Theoharides, T.C., 1995b. Increased number of substance P positive nerve fibers in interstitial cystitis. *Br. J. Urol.* 75, 744–750.
- Pang, X., Letourneau, R., Rozniecki, J.J., Wang, L., Theoharides, T.C., 1996a. Definitive characterization of rat hypothalamic mast cells. *Neuroscience* 73, 889–902.
- Pang, X., Boucher, W., Triadafilopoulos, G., Sant, G.R., Theoharides, T.C., 1996b. Mast cell and substance P-positive nerve involvement in a patient with both irritable bowel syndrome and interstitial cystitis. *Urology* 47, 436–438.
- Pang, X., Alexacos, N., Letourneau, R., Seretakis, D., Gao, W., Cochrane, D.E., Theoharides, T.C., 1998a. A neurotensin receptor antagonist inhibits acute immobilization stress-induced cardiac mast cell degranulation, a corticotropin-releasing hormone-dependent process. *J. Pharmacol. Exp. Ther.* 287, 307–314.
- Pang, X., Sant, G.R., Theoharides, T.C., 1998b. Altered expression of bladder mast cell growth factor receptor (c-kit) expression in interstitial cystitis. *Urology* 51, 939–944.
- Panula, P., Yang, H.Y., Costa, E., 1984. Histamine-containing neurons in the rat hypothalamus. *Proc. Natl. Acad. Sci. U. S. A.* 81, 2572–2576.
- Park, C.H., Joo, Y.E., Choi, S.K., Rew, J.S., Kim, S.J., Lee, M.C., 2003. Activated mast cells infiltrate in close proximity to enteric nerves in diarrhea-predominant irritable bowel syndrome. *J. Korean Med. Sci.* 18, 204–210.
- Parsons, C.L., Lilly, J.D., Stein, P., 1991. Epithelial dysfunction in non-bacterial cystitis (interstitial cystitis). *J. Urol.* 145, 732–735.
- Patella, V., de Crescenzo, G., Ciccirelli, A., Marino, I., Adt, M., Marone,

- G., 1995. Human heart mast cells: a definitive case of mast cell heterogeneity. *Int. Arch. Allergy Immunol.* 106, 386–393.
- Pedotti, R., DeVoss, J.J., Steinman, L., Galli, S.J., 2003. Involvement of both “allergic” and “autoimmune” mechanisms in EAE, MS and other autoimmune diseases. *Trends Immunol.* 24, 479–484.
- Peeker, R., Enerback, L., Fall, M., Aldenborg, F., 2000. Recruitment, distribution and phenotypes of mast cells in interstitial cystitis. *J. Urol.* 163, 1009–1015.
- Pollard, H., Bischoff, S., Llorens-Cortes, C., Schwartz, J.C., 1976. Histidine decarboxylase and histamine in discrete nuclei of rat hypothalamus and the evidence for mast-cells in the median eminence. *Brain Res.* 24 (118), 509–513.
- Pontari, M.A., Hanno, P.M., 1995. Interstitial cystitis. In: Walsh, P.C., Retik, A.B., Stamey, T.A., Vaughan, E.D., Wein, A.J. (Eds.), *Campbell’s Urology*, pp. 1–19 W.B. Saunders, New York.
- Pothoulakis, C., Castagliuolo, I., LaMont, J.T., 1998. Nerves and intestinal mast cells modulate responses to enterotoxins. *News Physiol. Sci.* 13, 58–63.
- Reuter, U., Bolay, H., Jansen-Olesen, I., Chiarugi, A., Sanchez del Rio, M., Letourneau, R., Theoharides, T.C., Waeber, C., Moskowitz, M.A., 2001. Delayed inflammation in rat meninges: implications for migraine pathophysiology. *Brain* 124, 2490–2502.
- Rivest, S., Laflamme, N., Nappi, R.E., 1995. Immune challenge and immobilization stress induce transcription of the gene encoding the CRF receptor in selective nuclei of the rat hypothalamus. *J. Neurosci.* 15, 2680–2695.
- Robbie-Ryan, M., Tanzola, M.B., Secor, V.H., Brown, M.A., 2003. Cutting edge: both activating and inhibitory Fc receptors expressed on mast cells regulate experimental allergic encephalomyelitis disease severity. *J. Immunol.* 170, 1630–1634.
- Roberts, F., Calcutt, C.R., 1983. Histamine and the hypothalamus. *Neuroscience* 9, 721–739.
- Rodewald, H.-R., Dessing, M., Dvorak, A.M., Galli, S.J., 1996. Identification of a committed precursor for the mast cell lineage. *Science* 271, 818–822.
- Rothrock, N.E., Lutgendorf, S.K., Kreder, K.J., Ratliff, T., Zimmerman, B., 2001. Stress and symptoms in patients with interstitial cystitis: a life stress model. *Urology* 57, 422–427.
- Rouleau, A., Dimitriadou, V., Trung Tuong, M.D., Newlands, G.F., Miller, H.R., Schwartz, J.C., Garbarg, M., 1997. Mast cell specific proteases in rat brain: changes in rats with experimental allergic encephalomyelitis. *J. Neural Transm.* 104, 399–417.
- Rowe, W.B., Nicot, A., Sharma, S., Gully, D., Walker, C.D., Rostene, W.H., Meaney, M.J., Quirion, R., 1997. Central administration of the neurotensin receptor antagonist, SR48692, modulates diurnal and stress-related hypothalamic–pituitary–adrenal activity. *Neuroendocrinology* 66, 75–85.
- Rozanski, A., Bairey, C.N., Krantz, D.S., Friedman, J., Resser, K.J., Morell, M., Hilton-Chalfen, S., Hestrin, L., Bietendorf, J., Berman, D.S., 1988. Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. *N. Engl. J. Med.* 318, 1005–1012.
- Rozniecki, J.J., Hauser, S.L., Stein, M., Lincoln, R., Theoharides, T.C., 1995. Elevated mast cell tryptase in cerebrospinal fluid of multiple sclerosis patients. *Ann. Neurol.* 37, 63–66.
- Rozniecki, J.J., Dimitriadou, V., Lambracht-Hall, M., Pang, X., Theoharides, T.C., 1999. Morphological and functional demonstration of rat dura mast cell–neuron interactions in vitro and in vivo. *Brain Res.* 849, 1–15.
- Saban, R., Gerard, N.P., Saban, M.R., Nguyen, N.B., DeBoer, D.J., Wer-shil, B.K., 2002. Mast cells mediate substance P-induced bladder inflammation through an NK(1) receptor-independent mechanism. *Am. J. Physiol., Renal. Physiol.* 283, F616–F629.
- Sant, G.R., 1991. Interstitial cystitis. *Monogr. Urol.* 12, 37–63.
- Secor, V.H., Secor, W.E., Gutekunst, C.-A., Brown, M.A., 2000. Mast cells are essential for early onset and severe disease in a murine model of multiple sclerosis. *J. Exp. Med.* 191, 813–821.
- Seebeck, J., Kruse, M.L., Schmidt-Choudhury, A., Schmidtmayer, J., Schmidt, W.E., 1998. Pituitary adenylate cyclase activating polypeptide induces multiple signaling pathways in rat peritoneal mast cells. *Eur. J. Pharmacol.* 352, 343–350.
- Schmaling, K.B., McKnight, P.E., Afari, N., 2002. A prospective study of the relationship of mood and stress to pulmonary function among patients with asthma. *J. Asthma* 39, 501–510.
- Sharma, H.S., Cervos-Navarro, J., Dey, P.K., 1991. Increased blood–brain barrier permeability following acute short-term swimming exercise in conscious normotensive young rats. *Neurosci. Res.* 10, 211–221.
- Sharma, H.S., Westman, J., Navarro, J.C., Dey, P.K., Nyberg, F., 1995. Probable involvement of serotonin in the increased permeability of the blood–brain barrier by forced swimming. An experimental study using Evans blue and <sup>131</sup>I-sodium tracers in the rat. *Behav. Brain Res.* 72, 189–196.
- Sieghart, W., Theoharides, T.C., Alper, S.L., Douglas, W.W., Greengard, P., 1978. Calcium-dependent protein phosphorylation during secretion by exocytosis in the mast cell. *Nature* 275, 329–331.
- Singh, L.K., Boucher, W., Pang, X., Letourneau, R., Seretakakis, D., Green, M., Theoharides, T.C., 1999a. Potent mast cell degranulation and vascular permeability triggered by urocortin through activation of CRH receptors. *J. Pharmacol. Exp. Ther.* 288, 1349–1356.
- Singh, L.K., Pang, X., Alexacos, N., Letourneau, R., Theoharides, T.C., 1999b. Acute immobilization stress triggers skin mast cell degranulation via corticotropin releasing hormone, neurotensin and substance P: a link to neurogenic skin disorders. *Brain Behav. Immun.* 13, 225–239.
- Skofitsch, G., Savitt, J.M., Jacobowitz, D.M., 1985. Suggestive evidence for a functional unit between mast cells and substance P fibers in the rat diaphragm and mesentery. *Histochemistry* 82, 5–8.
- Skultetyova, I., Tokarev, D., Jezova, D., 1998. Stress-induced increase in blood–brain barrier permeability in control and monosodium glutamate-treated rats. *Brain Res. Bull.* 45, 175–178.
- Slominski, A., Wortsman, J., 2000. Neuroendocrinology of the skin. *Endocr. Rev.* 21, 457–487.
- Slominski, A., Wortsman, J., Luger, T., Paus, R., Solomon, S., 2000. Corticotropin releasing hormone and proopiomelanocortin involvement in the cutaneous response to stress. *Physiol. Rev.* 80, 979–1020.
- Slominski, A., Wortsman, J., Pisarchik, A., Zbytek, B., Linton, E.A., Mazurkiewicz, J.E., Wei, E.T., 2001. Cutaneous expression of corticotropin-releasing hormone (CRH), urocortin, and CRH receptors. *FASEB J.* 15, 1678–1693.
- Spanos, C.P., Pang, X., Ligris, K., Letourneau, R., Alferes, L., Alexacos, N., Sant, G.R., Theoharides, T.C., 1977. Stress-induced bladder mast cell activation: implications for interstitial cystitis. *J. Urol.* 157, 669–672.
- Spanos, C., el-Mansoury, M., Letourneau, R., Minogiannis, P., Greenwood, J., Siri, P., Sant, G.R., Theoharides, T.C., 1996. Carbachol-induced bladder mast cell activation: augmentation by estradiol and implications for interstitial cystitis. *Urology* 48, 809–816.
- Spierings, E.L., 2003. Pathogenesis of the migraine attack. *Clin. J. Pain* 19, 255–262.
- Sundaram, K., Didolkar, A., Thau, R., Chaudhuri, M., Schmidt, F., 1988. Antagonists of luteinizing hormone releasing hormone bind to rat mast cells and induce histamine release. *Agents Actions* 25, 307–313.
- Suzuki, R., Furuno, T., McKay, D.M., Wolvers, D., Teshima, R., Nakanishi, M., Bienenstock, J., 1999. Direct neurite-mast cell communication in vitro occurs via the neuropeptide substance P. *J. Immunol.* 163, 2410–2415.
- Suzuki, M., Inaba, S., Nagai, T., Tatsuno, H., Kazatani, Y., 2003. Relation of C-reactive protein and interleukin-6 to culprit coronary artery plaque size in patients with acute myocardial infarction. *Am. J. Cardiol.* 91, 331–333.
- Tetlow, L.C., Woolley, D.E., 1995. Distribution, activation and tryptase/chymase phenotype of mast cells in the rheumatoid lesion. *Ann. Rheum. Dis.* 54, 549–555.
- Theoharides, T.C., 1983. Mast cells and migraines. *Perspect. Biol. Med.* 26, 672–675.
- Theoharides, T.C., 1990. Mast cells: the immune gate to the brain. *Life Sci.* 46, 607–617.

- Theoharides, T.C., 1996. The mast cell: a neuroimmunoendocrine master player. *Int. J. Tissue React.* 18, 1–21.
- Theoharides, T.C., 2002. Mast cells and stress—a psychoneuroimmunological perspective. *J. Clin. Psychopharmacol.* 22, 103–108.
- Theoharides, T.C., 2003. Dietary supplements for arthritis and other inflammatory conditions: key role of mast cells and benefit of combining anti-inflammatory and proteoglycan products. *Eur. J. Inflamm.* 1, 1–8.
- Theoharides, T.C., Douglas, W.W., 1978. Secretion in mast cells induced by calcium entrapped within phospholipid vesicles. *Science* 201, 1143–1145.
- Theoharides, T.C., Sant, G.R., 1994. The role of the mast cell in interstitial cystitis. *Urol. Clin. North Am.* 21, 41–53.
- Theoharides, T.C., Sieghart, W., Greengard, P., Douglas, W.W., 1980. Anti-allergic drug cromolyn may inhibit histamine secretion by regulating phosphorylation of a mast cell protein. *Science* 207, 80–82.
- Theoharides, T.C., Bondy, P.K., Tsakalos, N.D., Askenase, P.W., 1982. Differential release of serotonin and histamine from mast cells. *Nature* 297, 229–231.
- Theoharides, T.C., Dimitriadou, V., Letourneau, R.J., Rozniecki, J.J., Vliagofitis, H., Boucher, W.S., 1993. Synergistic action of estradiol and myelin basic protein on mast cell secretion and brain demyelination: changes resembling early stages of demyelination. *Neuroscience* 57, 861–871.
- Theoharides, T.C., Sant, G.R., El-Mansoury, M., Letourneau, R.J., Ucci Jr., A.A., Meares Jr., E.M. 1995a. Activation of bladder mast cells in interstitial cystitis: a light and electron microscopic study. *J. Urol.* 153, 629–636.
- Theoharides, T.C., Spanos, C.P., Pang, X., Alferes, L., Ligris, K., Letourneau, R., Rozniecki, J.J., Webster, E., Chrousos, G., 1995b. Stress-induced intracranial mast cell degranulation. A corticotropin releasing hormone-mediated effect. *Endocrinology* 136, 5745–5750.
- Theoharides, T.C., Pang, X., Letourneau, R., Sant, G.R., 1998a. Interstitial cystitis: a neuroimmunoendocrine disorder. *Ann. N.Y. Acad. Sci.* 840, 619–634.
- Theoharides, T.C., Singh, L.K., Boucher, W., Pang, X., Letourneau, R., Webster, E., Chrousos, G., 1998b. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its pro-inflammatory effects. *Endocrinology* 139, 403–413.
- Theoharides, T.C., Letourneau, R., Patra, P., Hesse, L., Pang, X., Boucher, W., Mompoin, C., Harrington, B., 1999. Stress-induced rat intestinal mast cell intragranular activation and inhibitory effect of sulfated proteoglycans. *Dig. Dis. Sci.* 144 (Suppl. 8), 87S–93S.
- Theoharides, T.C., Patra, P., Boucher, W., Letourneau, R., Kempuraj, D., Chiang, G., Jeudy, S., Hesse, L., Athanasiou, A., 2000. Chondroitin sulfate inhibits connective tissue mast cells. *Br. J. Pharmacol.* 131, 10139–10149.
- Theoharides, T.C., Kempuraj, D., Sant, G.R., 2001a. Mast cell involvement in interstitial cystitis: a review of human and experimental evidence. *Urology* 57 (6 Suppl. 1), 47–55.
- Theoharides, T.C., Alexandrakis, M., Kempuraj, D., Zytinas, M., 2001b. Anti-inflammatory actions of flavonoids and structural requirements for new design. *Int. J. Immunopathol. Pharmacol.* 14 (3), 119–127.
- Theoharides, T.C., Stein, M., Spear, K., Hauser, S., 2002. A pilot, double-blind, placebo-controlled clinical trial using hydroxyzine in remitting–relapsing multiple sclerosis (RR-MS). *Pharmacologist* 44, A165.
- Theoharides, T.C., Donelan, J., Kandere-Grzybowska, K., 2004. Stress, corticotropin-releasing hormone and brain mast cells: a new model for the pathogenesis of migraines. *Brain Res.* (In press).
- Thomason, B.T., Brantley, P.J., Jones, G.N., Dyer, H.R., Morris, J.L., 1992. The relation between stress and disease activity in rheumatoid arthritis. *J. Behav. Med.* 15, 215–220.
- Tompkins, S.M., Miller, S.D., 2002. An array of possibilities for multiple sclerosis. *Nat. Med.* 8, 451–453.
- Toms, R., Weiner, H.L., Johnson, D., 1990. Identification of IgE-positive cells and mast cells in frozen sections of multiple sclerosis brains. *J. Neuroimmunol.* 30, 169–177.
- Toyoda, M., Makino, T., Kagoura, M., Morohashi, M., 2000. Immunolocalization of substance P in human skin mast cells. *Arch. Dermatol. Res.* 292, 418–421.
- Tuomisto, L., Kilpeläinen, H., Riekkinen, P., 1983. Histamine and histamine-N-methyltransferase in the CSF of patients with multiple sclerosis. *Agents Actions* 13, 255–257.
- Uzuki, M., Sasano, H., Muramatsu, Y., Totsune, K., Takahashi, K., Oki, Y., Iino, K., Sawai, T., 2001. Urocortin in the synovial tissue of patients with rheumatoid arthritis. *Clin. Sci.* 100, 577–589.
- van der Kleij, H.P., Ma, D., Redegeld, F.A., Kraneveld, A.D., Nijkamp, F.P., Bienenstock, J., 2003. Functional expression of neurokinin 1 receptors on mast cells induced by IL-4 and stem cell factor. *J. Immunol.* 171, 2074–2079.
- van Haaster, C.M.C.J., Engels, W., Lemmens, P.J.M.R., Hornstra, G., van der Vusse, G.J., Heemskerk, J.W.M., 1995. Differential release of histamine and prostaglandin D2 in rat peritoneal mast cells; roles of cytosolic calcium and protein tyrosine kinases. *Biochim. Biophys. Acta* 1265, 79–88.
- Van Loveren, H., Kops, S.K., Askenase, P.W., 1984. Different mechanisms of release of vasoactive amines by mast cells occur in T cell-dependent compared to IgE-dependent cutaneous hypersensitivity responses. *Eur. J. Immunol.* 14, 40–47.
- Vliagofitis, H., Dimitriadou, V., Boucher, W., Rozniecki, J.J., Correia, I., Raam, S., Theoharides, T.C., 1992. Estradiol augments while tamoxifen inhibits rat mast cell secretion. *Int. Arch. Allergy Immunol.* 98, 398–409.
- von Hertzen, L.C., 2002. Maternal stress and T-cell differentiation of the developing immune system: possible implications for the development of asthma and atopy. *J. Allergy Clin. Immunol.* 109, 923–928.
- Warren, S., Greenhill, S., Warren, K.G., 1982. Emotional stress and the development of multiple sclerosis: case control evidence of a relationship. *J. Chronic. Dis.* 35, 821–831.
- Webster, E.L., Barrientos, R.M., Contoreggi, C., Isaac, M.G., Ligier, S., Gabry, K.E., Chrousos, G.P., McCarthy, E.F., Rice, K.C., Gold, P.W., Sternberg, E.M., 2002. Corticotropin releasing hormone (CRH) antagonist attenuates adjuvant induced arthritis: role of CRH in peripheral inflammation. *J. Rheumatol.* 29, 1252–1261.
- Weston, A.P., Biddle, W.L., Bhatia, P.S., Miner Jr., P.B. 1993. Terminal ileal mucosal mast cells in irritable bowel syndrome. *Dig. Dis. Sci.* 38, 1590–1595.
- Wiesner-Menzel, L., Schulz, B., Vakilzadeh, F., Czarnetzki, B.M., 1981. Electron microscopical evidence for a direct contact between nerve fibers and mast cells. *Acta Derm. - Venereol. (Stockh)* 61, 465–469.
- Williams, C.L., Peterson, J.M., Villar, R.G., Burks, T.F., 1987. Corticotropin-releasing factor directly mediates colonic responses to stress. *Am. J. Physiol.* 253, 582–586.
- Williams, R.M., Bienenstock, J., Stead, R.H., 1995. Mast cells: the neuro-immune connection. *Chem. Immunol.* 61, 208–235.
- Woolley, D.E., 1995. Mast cells in the rheumatoid lesion—ringleaders or innocent bystanders. *Ann. Rheum. Dis.* 54, 533–534.
- Xiang, Z., Nilsson, G., 2000. IgE receptor-mediated release of nerve growth factor by mast cells. *Clin. Exp. Allergy* 30, 1379–1386.
- Yamatodani, A., Maeyama, K., Watanabe, T., Wada, H., Kitamura, Y., 1982. Tissue distribution of histamine in a mutant mouse deficient in mast cells: clear evidence for the presence of non-mast-cell histamine. *Biochem. Pharmacol.* 31, 305–309.
- Woolley, D.E., 2003. The mast cell in inflammatory arthritis. *N. Engl. J. Med.* 348, 1709–1711.
- Zhao, X.J., McKerr, G., Dong, Z., Higgins, C.A., Carson, J., Yang, Z.Q., Hannigan, B.M., 2001. Expression of oestrogen and progesterone receptors by mast cells alone, but not lymphocytes, macrophages or other immune cells in human upper airways. *Thorax* 56, 205–211.
- Zhuang, X., Silverman, A.-J., Silver, R., 1996. Brain mast cell degranulation regulates blood–brain barrier. *J. Neurobiol.* 31, 393–403.