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EDITORIAL

INHIBITOR EFFECT OF ANTIOXIDANT FLAVONOIDS QUERCITIN, AND CAPSAICIN IN MAST CELL INFLAMMATION

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Mast cells are essential not only for allergies but also for innate and acquired immunity, autoimmunity and inflammation, and they are recognized as a new type of immunoregulatory cells capable of producing different cytokines. Natural compounds have long been recognized to possess anti-inflammatory, antioxidant and anticancergenic activity. Quercitin is an inhibitor for mast cells and is a potent antioxidant, cytoprotective and anti-inflammatory compound and has a negative effect on intracellular regulator signal events initiated by FceRI receptor cross-linking and other activating receptors on mast cells. These observations candidate quercitin as a therapeutic compound in association with other therapeutic molecules. Capsaicin is a compound derived from peppers, especially capsicum, and is involved in stimulating circulation aiding digestion and relieving pain. Capsaicin receptor sub type I (VRI) is expressing in neurons and is present in a number of brain nuclei and in non-neuronal tissues, mediating inflammatory response. Capsaicin is involved in migraine, allergic symptoms, arthritis pain and gastric secretion. In this paper we review the biological effects of quercitin and capsaicin.

Mast cells are characterized by metachromasia, as demonstrated by the use of basic dyes, such as Giemsa's reagent and toluidine blue. Mature human mast cells are tissue-residing, key effector cells of immediate allergic reactions (1). Moreover, mast cells have been recognized as a potent cellular source

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of multiple cytokines, suggesting an important role in immunoregulation and host defence (2). Mast cells have long been recognized as the principal cell type that initiates the inflammatory response characteristic of acute allergic type 1 reactions (3).

Mast cells are recognized as a new type of immunoregulatory cells capable of producing different cytokines. Mast cells accumulate in the stroma of a variety of inflamed and transformed tissues in response to locally produced chemotactic factors for monocytes/mast cells, such as RANTES and MCP-1 (4). Human mast cells produce pro-inflammatory PGD2 that may be up-regulated following triggering with IgE-independent agonists such as bacteria, whereas activation by IgE receptor cross-linking may result in the expression of Th2-type cytokines such as IL-4 which enhances the expression of Th2-type cytokines and down-regulates pro-inflammatory cytokines (5).

Mast cells can be immunologically activated by IgE through their Fc receptors, as well as by neuropeptides and cytokines to secrete mediators and they play an important role in reactions of allergic disease (6). Electron microscopy study of mast cells in allergic tissue show irregularly-shaped cells with long and interdigitating cytoplasmatic villi. In airways, mast cells lie adjacent to nerves, blood vessels and lymphatics, which highlights their pivotal importance in regulating allergic inflammatory processes (7). Mast cells release substances such as histamine, leukotrienes B4, C4 and D4, 5-hydroxyeicosatetraenoic acid, prostaglandin D_2 (PGD_2), Platelet Activating Factor (PAF) and heparin, and contain tryptase and chymase (8). Tryptases are expressed by most human mast cells and are divided into two groups: alpha or beta. Beta tryptase appears to be the major type stored in secretory granules of mast cells, while alpha is the main type expressed in basophils (9). Protease-activated receptors (PARs) are G-protein-coupled receptors activated by proteases, including tryptase. Several studies suggest a role for tryptase in allergic diseases and inflammatory reactions mediated by human mast cells by stimulating PARs (10). Among mast cell products, the protease tryptase could be associated with neurodegenerative processes through the activation of specific receptors (PARs) expressed in the brain, while interleukin-6 likely causes neurodegeneration and exacerbates dysfunction induced by other cytokines, or it could have a protective effect against demyelinisation (11).

Mast cells are essential not only for allergies but also for innate and acquired immunity, autoimmunity and inflammation (12). Mast cells can accumulate at inflammatory sites in response to the specific C-C chemokine Regulated upon Activation, Normal T-Cell Expressed and Secreted (RANTES) and MCP-1 (13). Since ancient times all around the world, humans have found remedies in herbs and plants. Patients often seek complementary therapies including herbal medicines due to reasons such as unsatisfactory effects, high cost, non-availability, or adverse effects of conventional medicines. Natural compounds have long been recognized to possess anti-inflammatory, anti-oxidant, anti-allergic, hepatoprotective, anti-thrombotic, anti-viral and anti-carcinogenic activities (14).

Quercetin

Quercetin is an inhibitor of immunological and

Table I. *Biological effects of capsaicin.*

Digestive aid (stimulates gastric secretions)
Arthritis pain reliever
Raises metabolic rate
Reduces allergic symptoms (hay fever-type allergies)
Prevents migraine headaches

non-immunological stimulus for mast cells and is a potent antioxidant, cytoprotective and anti-inflammatory compound capable of inhibiting histamine and some cytokines released from several cell types (15). The flavonoid quercetin has a variety of functions including anti-allergic activities, and is known to inhibit histamine release from human basophils and murine mast cells (16). Quercetin has a negative effect on intracellular regulator signaling events initiated by FcεRI cross-linking and other activating receptors on mast cells (17). Increased secretion of mast cell tryptase in certain disorders, such as bronchial asthma, may augment neurogenic inflammation. In spite of this, it is not clear whether quercetin is capable of directly inhibiting tryptase or IL-6 release from basophilic cells. One study has shown that quercetin, a natural compound able to act as an inhibitor of mast cell secretion, causes a decrease in the release of tryptase and IL-6 and the down-regulation of histidine decarboxylase (HDC) mRNA from human mast cell (HMC)-1. As quercetin dramatically inhibits mast cell tryptase and IL-6 release and HDC mRNA transcription by HMC-1 cell line, these observations nominate quercetin as a therapeutic compound in association with other therapeutic molecules for neurological diseases mediated by mast cell degranulation.

It has been found that the potent antioxidant, cytoprotective and anti-inflammatory properties of quercetin acts also as an inhibitor of tryptase and IL-6 production. HMC-1 cells treated with quercetin provoke a significant inhibition of tryptase and IL-6 release compared to the calcium ionophore A23187 or anti-IgE stimulation. Moreover, the addition of quercetin determines an inhibition of HDC mRNA expression in HMC-1 cells. It has been found that actinomycin D, a drug that blocks the transcription of new RNA, and cycloheximide, a protein synthesis inhibitor, abolishes the reduction of HDC mRNA in cells treated overnight with quercetin. These results suggest that HDC mRNA down-regulated by quercetin is a complex process that could require the transcription and translation of one or several genes to decrease HDC mRNA expression. Quercetin might have such modulating properties on mast cells: as mast cell secretion products have some effects that promote and others that suppress inflammation, quercetin may reduce the release of pro-inflammatory mediators. The inhibition of HDC mRNA transcription and tryptase and IL-6 generation by quercetin on mast cells may be useful in many pathological conditions associated with acute and chronic inflammation status.

Capsaicin

Capsaicin is a chemical compound derived from peppers, specifically capsicum, also known as cayenne. Capsaicin is the ingredient found in different types of hot peppers, such as cayenne peppers, that makes the peppers spicy hot. Capsaicin has been used for centuries as a folk medicine for stimulating circulation, aiding digestion and relieving pain (topically). It may also have potential in treating neuropathic pain. Various spice-derived nutraceuticals have always been used to improve taste and color and as a preservative, and are now also used for prevention and treatment of a wide variety of chronic inflammatory diseases, including cancer.

Pharmacologic therapies for pain control include tricylic antidepressants, anticonvulsants, analgesics, and capsaicin. Capsaicin is used to relieve neuropathic pain, uremic pruritus, and bladder over-activity. By activating specific receptors on primary nociceptive afferents, inflammatory mediators are essential for the initiation and maintenance of peripheral sensitization (1). Vanilloid (capsaicin) receptor subtype 1 (VR1) integrates multiple noxious stimuli on peripheral terminals of primary sensory neurons. In addition, VR1-expressing neurons are present in a number of brain nuclei and in non-neuronal tissues. The expression of VR1 is down-regulated during vanilloid therapy, which might have a pivotal role in desensitization. Evidence suggests an altered VR1 expression in various disease states. The existence of vanilloid receptors in several brain nuclei as well as in non-neuronal tissues predicts novel, innovative therapeutic indications for vanilloids. In addition, abundant evidence has demonstrated that vanilloid is also modulated by numerous inflammatory mediators, including chemokines and cytokines (2). This recognition may provide novel insights into pathogenesis and may be useful in diagnosis. However, these findings also suggest that vanilloids might cause side-effects.

Pharmacologic therapies for pain control may also

include capsaicin. Capsaicin is a specific neurotoxin for type C non-myelinated vesical afferent fibres involved in the transmission of nociceptive stimuli and reorganization of voiding reflexes in disease. Capsaicin is a potent anti-inflammatory compound, and has been proposed as a fighter of chronic, subclinical inflammation. Capsaicin as a blocking agent of neuropeptides, blocks the axon reflex and may exert a curative effect on allergic rhinitis. A small pharmacological effect on clinical histamine dose response was found.

However, because capsaicin may induce bronchoconstriction, people suffering from chronic obstructive lung disease may be hypersensitive to it. Although the results of one study indicate that asthmatics do not develop additional bronchoconstriction following inhalation of capsaicin.

The human nuclear transcription factors (NTFs), two of which - activator protein 1 (AP-1) and NF-kappa B - are especially important targets when it comes to prevention of cancer and premature aging of organs. Each of these NTFs can be "activated" by ultraviolet light and free radicals: a result that produces a pro-inflammatory chain reaction that promotes premature aging and a wide variety of degenerative diseases. As it turns out, nature offers several effective NTF-activation blockers, including the capsaicin in chilies.

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