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Immunomodulation of mast cells by nutrients☆

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ABSTRACT

In the past decades an increasing prevalence of allergic disorders was observed in industrialized countries. Thus, it is necessary to develop adequate therapeutic and preventive strategies. Many of the conservative strategies possess diverse harmful side effects. Therefore agents with fewer side effects and a better compliance among afflicted patients would be of interest. Especially substances with natural origin acting immunomodulatory on mast cells – the key effector cells of allergic diseases – could be used. Among them there are components of the daily diet such as distinct fatty acids and amino acids as well as a range of secondary plant substances such as carotenoids, flavonoids and spices. These nutritional substances could be applied as *nutraceuticals* in the therapy of mast cell associated diseases. Many of these substances show inhibitory influences on the release of prestored mast cell mediators such as histamine or *de novo* expression of mast cell mediators such as cytokines and eicosanoids which are involved in the pathogenesis of mast cell associated inflammatory conditions like allergic reactions.

1. Introduction

Mast cells are key effector cells of type I allergic reactions as well as of other inflammatory processes. Hereby, mast cells act proinflammatory by releasing a wide range of inflammatory mediators upon activation. These are pre-stored ones found in the mast cells' granula like histamine and proteases, but also *de novo* synthesized mediators like cytokines and eicosanoids. Mast cells can be activated by different stimuli, whereby the stimulation *via* the high-affinity IgE-receptor FcεRI is the best established activation signal. Aggregation of IgE and subsequent FcεRI on mast cells initiates type I allergic reactions (Bischoff, 2007; Kalesnikoff and Galli, 2008; Kopeć et al., 2006). Lipid rafts are known as putative platforms for FcεRI aggregation to which FcεRI is translocated after binding of the antigen to the surface IgE. Lipid rafts are detergent-resistant micro domains of the cell membrane being important sites for protein-tyrosine-kinase-mediated protein–protein interactions making them to platforms for the induction of several receptor signaling pathways (Gilfillan and Tkaczyk, 2006; Kalesnikoff and Galli, 2008). The antigen-crosslinking of these IgE-FcεRI complexes leads to the activation of mast cells. After stimulation *via* FcεRI an intracellular signaling cascade is initiated involving among others signaling proteins like Fyn and Lyn kinase as earlier signals in the cascade and PKC, PI3K, MAPK, and Akt as more down-stream signaling proteins (Kopeć et al., 2006). This signaling cascade initiates degranulation as well as *de novo* synthesis of lipid mediators, cytokines and others inducing the allergic response (Kopeć et al., 2006; Sakai et al., 2009).

In developed countries, the number of patients suffering from allergic diseases like atopic dermatitis or allergic rhinoconjunctivitis increased up to 25–30% over the past decades (Gupta et al., 2007). It is therefore necessary to develop new therapeutic or preventive agents having fewer side effects than the present conservative therapy. In this context "nutraceuticals" can be of interest. The term "nutraceutical" was derived from "nutrition" and "pharmaceutical" by DeFelice in 1989 and is defined as "a food or part of a food that provides medical or health benefits, including the prevention and treatment of a disease" (DeFelice, 1995). Nutraceuticals can be isolated nutrients, herbal products, processed products such as beverages and soups, as well as dietary supplements (DeFelice, 1995). *E.g.* for polyphenols – main active components in plants – as polyphenols from green tea, it is known that they can influence diverse immune cells like dendritic cells and Th2-cells influencing thereby allergic reactions (Gong and Chen, 2003; Tomita et al., 2002). Diverse naturally occurring secondary plant substances and other selected dietary substances are known for their effects on mast cell activation. Among them are anti-oxidative plant substances like carotenoids and flavonoids, but also different kinds of spices, as well as dietary substances like distinct fatty acids and

Abbreviations: AA, arachidonic acid; BMMC, bone marrow-derived mast cells; CBMC, cord blood-derived mast cells; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EGCG, epigallocatechin-3-gallate; hiMC, human intestinal mast cells; IONO/PMA, calcium ionophore/phorbol-12-myristate-13-acetate; LT, leukotriene; PCA, percutaneous anaphylactic reactions; PG, prostaglandin; PUFA, polyunsaturated fatty acids.

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amino acids. Nutraceuticals could be a beneficial alternative or additional kind of therapy as they are associated with reduced side effects and a better compliance among patients.

This review gives an overview of the immunomodulatory capacities of selected food components on mast cell activation *in vitro* and in context of mast cell associated diseases especially type I allergic reactions *in vivo*. The immunomodulatory activity of these nutrients could be probably used by applying them as nutraceuticals in context of diverse mast cell associated diseases like allergy through the down-regulation of mast cell activation.

2. Influence of selected nutrients on mast cell activation

2.1. Fatty acids

Fatty acids are incorporated in cell membranes and can probably influence mediator production and secretion of mast cells (Gueck et al., 2004a,b). Incubation of the human mast cell lines LAD-2 and HMC-1 with the n-6 long-chain polyunsaturated fatty acids (PUFA) arachidonic acid (AA) or with the n-3 long-chain PUFAs eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) influenced mast cell activation. All three fatty acids had no effect on IgE-mediated degranulation of LAD-2 cells. However, AA increased secretion of prostaglandin (PG) D_2 and TNF of calcium ionophore/phorbol-12-myristate-13-acetate (IONO/PMA) activated HMC-1 cells and EPA and DHA inhibited IL-4 and IL-13 secretion (Van den Elsen et al., 2012). Suppression of IL-4 and IL-13 secretion was hereby correlated with a reduced generation of ROS. The suppression of MAPK, but not NFκB, downstream of ROS decreased IL-13 secretion in activated HMC-1 cells. This gives a hint that the n-6 long-chain PUFA AA enhances pro-inflammatory mediator production by mast cells, whereas n-3 long-chain PUFAs EPA and DHA affect the pro-inflammatory mast cell action in an inhibitory way (Van den Elsen et al., 2012). This is in accordance with the proposed correlation between the typical Western diet with a reduced dietary intake of n-3 long-chain PUFAs from oily fish together with the increased intake of n-6 long-chain PUFAs from vegetable oils and the increased incidence of allergic diseases in the last decades (Van den Elsen et al., 2012). In addition to these results, the canine atopic dermatitis represented by a canine mastocytoma cell line (C2) can be differentially influenced by treatment with diverse fatty acids. GLA (n-6) increased tryptase activity and decreased histamine release in stimulated C2 cells and DHA (n-3) reduced PGE_2 production. α-linolenic acid (n-3) caused a reduction of tryptase activity, PGE_2 production as well as histamine release, whereas linoleic acid or AA (n-6) increased them (Gueck et al., 2003, 2004a,b). Ju et al. (1996) primed rats intraperitoneally with β-lactoglobulin to induce reagenic antibody and treated them with a diet rich in n-6 linoleic acid, saturated fatty acids, monounsaturated fatty acids or n-3 PUFAs. The rats treated with the linoleic rich diet showed a suppressed circulatory release of rat chymase II being relevant as indicator for degranulation of mucosal mast cells in the intestine (Ju et al., 1996). The underlying mechanism could be an enrichment of linoleic acid in the mast cell membrane altering the membrane structure and resulting in a reduced number and/or affinity of IgE receptors. But also a direct inhibitory effect of linoleic acid or its metabolites on IgE-mediated degranulation could be possible (Ju et al., 1996).

2.2. Amino acids

We have recently shown that a combined challenge of antigen-stimulated human mast cells isolated from intestinal tissue with pharmacological doses of the amino acids arginine and glutamine reduced leukotriene (LT) C_4 secretion, but not release of β-hexosamindase (Lechowski et al., 2013). In addition, the treatment with high doses of both amino acids resulted in a decreased expression of the chemokines CCL2, CCL4, CXCL8, and TNF. The mechanism of action based on a decreased activation of MAPK ERK, p38, and JNK as well as of Akt. This is conform to the above mentioned influences on expression and release of mediators such as LTC_4, TNF and CXCL8 in response to IgE dependent activation as they are – at least in part – regulated by activation of p38, ERK and Akt (Lechowski et al., 2013).

2.3. Carotenoids

Dietary carotenoids represent a class of natural pigments with tetraterpene structure possessing diverse biological functions such as anti-oxidative and anti-inflammatory capacities. Carotenoids also show beneficial activities concerning immune diseases like asthma or atopic dermatitis (Sakai et al., 2009). Fucoxanthin, astaxanthin, zeaxanthin and β-carotene (10 or 20 μM) significantly inhibited the antigen-induced degranulation – measured as release of β-hexosaminidase – of the rat basophilic leukemia mast cell line RBL-2H3 as well as mouse bone marrow-derived mast cells (BMMC) in a similar manner (Sakai et al., 2009). These carotenoids thereby act by inhibiting the antigen-induced FcεRI aggregation, resulting in a reduced activation of PKC-β, decreased phosphorylation of the downstream signaling molecules Fyn and Lyn kinase, and lower influx of intracellular Ca^{2+} (Sakai et al., 2009). Additionally to the effect on FcεRI aggregation, the mentioned carotenoids also inhibit the antigen-induced FcεRI translocation to lipid rafts – the putative platforms of FcεRI aggregation (Sakai et al., 2009). The molecular length of dihydroxycarotenoids matches the thickness of the phosphatidylcholine bilayer, and lutein and zeaxanthin probably are orientated in a perpendicular manner to the membrane surface, β-carotene can be orientated parallel or perpendicularly (Wisniewska et al., 2006). The carotenoid treatment of RBL-2H3 cells causes no visual disruption of lipid rafts, but probably modifies their function as the carotenoids locate in the cell membrane and therefore inhibit their translocation (Sakai et al., 2009). Other members of the terpene family, the monoterpenes geraniol and β-citronellol showed no inhibitory effect on β-hexosaminidase release and on FcεRI aggregation in RBL-2H3 cells assuming that this depends on their differences in chain length (Sakai et al., 2009).

The oral administration of 2–20 mg/kg β-carotene to BALB/c mice being immunized with ovalbumin (OVA) intraperitoneally resulted in a down-regulation of OVA-specific serum IgE levels and inhibited the type I allergic response. This proposes an anti-allergic effect of β-carotene (Sato et al., 2004). In addition to that, Sato et al. (2010) have demonstrated that a diet high in α- and β-carotene inhibited oral OVA sensitization and development of food allergies in mice. Serum titers of OVA-specific IgE and IgG1 and IgG2a were inhibited by α- and β-carotene treatment by about 50–60% and 80–90%, respectively. Moreover, the reduction in body temperature and the rise of serum histamine levels being associated with systemic anaphylaxis were inhibited as well. These results propose a probable use of a diet high in carotenoids in preventing the development of food allergies (Sato et al., 2010).

2.4. Flavonoids

Flavonoids are a molecular family of naturally occurring polyphenolic plant substances with anti-oxidative, anti-cancer and anti-inflammatory properties. They are naturally found in fruits, vegetables, herbs, nuts, spices and red wine. One group of flavonoids – the flavonols – is known for the beneficial effects on mast cells. Park et al. (2008) showed that the flavonols fisetin, kaempferol, myricetin, quercetin and rutin inhibited the IgE-mediated as well as the unspecific IONO/PMA-mediated histamine release and intracellular calcium elevation in RBL-2H3 cells. Human

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