REVIEW

# Nutraceutical Aid for Allergies – Strategies for Down-Regulating Mast Cell Degranulation

#### Mark F McCarty<sup>1</sup> Aaron Lerner 10<sup>2</sup> James J DiNicolantonio<sup>3,4</sup> Carina Benzvi<sup>2</sup>

<sup>1</sup>Catalytic Longevity Foundation, San Diego, CA, USA; <sup>2</sup>Chaim Sheba Medical Center, The Zabludowicz Research Center for Autoimmune Diseases, Tel Hashomer, Israel; <sup>3</sup>Saint Luke's Mid America Heart Institute, Kansas City, MO, USA; <sup>4</sup>Advanced Ingredients for Dietary Products, AIDP, City of Industry, CA, USA Abstract: Interactions of antigens with the mast cell FceRI-IgE receptor complex induce degranulation and boost synthesis of pro-inflammatory lipid mediators and cytokines. Activation of spleen tyrosine kinase (Syk) functions as a central hub in this signaling. The tyrosine phosphatase SHP-1 opposes Syk activity; stimulation of NADPH oxidase by FccRI activation results in the production of oxidants that reversibly inhibit SHP-1, up-regulating the signal from Syk. Activated AMPK can suppress Syk activation by the FccRI receptor, possibly reflecting its ability to phosphorylate the FceRI beta subunit. Cyclic GMP, via protein kinase G II, enhances the activity of SHP-1 by phosphorylating its C-terminal region; this may explain its inhibitory impact on mast cell activation. Hydrogen sulfide (H<sub>2</sub>S) likewise opposes mast cell activation; H2S can boost AMPK activity, up-regulate cGMP production, and trigger Nrf2-mediated induction of Phase 2 enzymes - including heme oxygenase-1, whose generation of bilirubin suppresses NADPH oxidase activity. Phycocyanobilin (PCB), a chemical relative of bilirubin, shares its inhibitory impact on NADPH oxidase, rationalizing reported anti-allergic effects of PCB-rich spirulina ingestion. Phase 2 inducer nutraceuticals can likewise oppose the up-regulatory impact of NADPH oxidase on FccRI signaling. AMPK can be activated with the nutraceutical berberine. Highdose biotin can boost cGMP levels in mast cells via direct stimulation of soluble guanylate cyclase. Endogenous generation of  $H_2S$  in mast cells can be promoted by administering N-acetylcysteine and likely by taurine, which increases the expression of  $H_2S$ -producing enzymes in the vascular system. Mast cell stabilization by benifuuki green tea catechins may reflect the decreased surface expression of FceRI.

**Keywords:** nutraceuticals, mast cell, degranulation, allergy, FccRI-IgE receptor, hydrogen sulfide, phycocyanobilin, berberine, biotin, lipoic acid

# Introduction

Pharmacological strategies are most commonly employed to control mast cell degranulation and its pathogenic consequences. This essay deals with nutraceutical strategies, which may have analogous therapeutic potential. The functions of mast cells and the molecular biology underlying mast cell degranulation will first be described.

# Contemporary Insights into Mast Cell Functions

Mast cell degranulation plays a key role in many human health disorders – not exclusively in allergies. The clinical presentation is wide, involving respiratory, neurologic, digestive, cardiovascular, cutaneous and even musculoskeletal symptoms.<sup>1</sup> Mast cells contribute to the pathogenesis of infection, cancer,

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Correspondence: Aaron Lerner Chaim Sheba Medical Center, The Zabludowicz Research Center for Autoimmune Diseases, Tel Hashomer, 5262000, Israel Tel +972-525-919484 Email aaronlerner1948@gmail.com cardiovascular and many other systemic diseases.<sup>2</sup> Notably, not only in pathologic conditions, they can play an immunomodulatory role, by secreting anti-anti-inflammatory mediators, and thereby impacting the inter-action between the immune cells and the environment.<sup>1–3</sup>

Mast cells are endowed with a wide range of plasma membrane receptors, enabling them to sense and react to a plethora of stimuli. The chief receptor triggering mast cell degranulation is the high-affinity IgE receptor FceRI (Figure 1). A more recently described mast cell receptor capable of provoking degranulation is the Mas-related G protein-coupled receptor X2 (MRGPRX2), which responds to a range of basic peptides and small proteins, resulting in allergic or neurologic inflammations, pain and itch; hence, there are more receptors that react to drugs, cytokines, complement anaphylatoxins, physical triggers and physical stimuli.<sup>1,4</sup> Upon sensing endogenous or exogenous danger signals, the activated mast cell releases mediators by three mechanisms. The immediate and rapid one is exocytosis of secretory granules containing pre-synthesized molecules, including histamine, various proteases, heparin, cysteinyl leukotrienes, prostaglandins, and certain proteoglycans. In the second phase, de novosynthesized cytokines, chemokines, interferons and several growth factors can be released independently of the degranulation process. Finally, activated mast cells can secrete extracellular vesicles, such as exosomes, thereby exteriorizing cellular proteins, enzymes, RNAs and miRNAs to the extracellular compartment.<sup>1</sup>

# Mast Cell Degranulation Process

Mast cells can assume a migratory or a secretory behavior, depending on their actin conformation. The secretory actin phenotype supports mobility and exocytosis, in which diaphanous-related formmin, mDia1, plays a major role in intracellular actin rearrangement.<sup>1</sup> Upon reaching its destination and encountering a secretagogue, mast cell degranulation can be executed in three different modes: full, partial, or the kiss-and-run phenomenon. In the full pathway, the granules can fuse completely with the plasma membrane, in the partial one, they form multiple granules fusion and creating a channel, and the third one implies a transiently fuse with the membrane, releasing part of their content. An additional means of degranulation has been discovered by electron microscopy, namely, piecemeal degranulation. Secretory granules can bud, producing vesicles that are transported to and fused with the plasma membrane.<sup>5</sup> These varying mechanisms whereby mast cells can release their contents determine the dynamics, intensity and the outcome of degranulation.<sup>1</sup>

A schematic presentation of the mast cells activation is presented in Figure 1.

# An Outline of FcERI Receptor Signaling

The FccRI receptor, whose activation triggers mast cell degranulation and increased production of lipid and cytokine pro-inflammatory mediators, is a heterotetramer that binds tightly to extracellular IgE.<sup>6,7</sup> The binding of this IgE to specific antigens triggers crosslinking of two RceRI receptor complexes such that src-family tyrosine kinase Lyn bound to each complex can auto-transphosphorylate. These phosphorylations, in turn, enable Lyn to phosphorvlate tyrosine residues on the  $\gamma$  subunit of the FceRI complex; this enables spleen tyrosine kinase (Syk) to bind to this subunit via its SH2 domain, and this bound Syk is then activated via phosphorylation by Lyn. Activated Syk then phosphorylates multiple tyrosines on a nearby LAT (linker for activated T cells) protein, enabling various other proteins to bind to LAT via their SH2 domains and to promote assembly of a complex signaling platform. Some of these proteins are also phosphorylated by Syk. The resulting signaling platform results in downstream activation of phospholipase  $C-\gamma$ , phosphatidylinositol-3-kinase (PI3K), IkB kinase, the MAP kinases ERK, JNK, and p38, and NADPH oxidase.<sup>6-8</sup> These collaborate to promote mast cell degranulation, while boosting synthesis of pro-inflammatory cytokines and lipid mediators. Although the src-family tyrosine kinase Fyn can substitute for Lyn in some of its signaling duties, it is clear that activation of Syk plays a fundamental and essential role in driving mast cell activation.9,10

Tyrosine kinase-mediated signaling is opposed and controlled by tyrosine phosphatase activities. Src homology region 2 domain-containing phosphatase 1 (SHP-1) has been shown in mast cells to oppose antigen-induced FccRI signaling;<sup>11–14</sup> it reverses tyrosine phosphorylations conferred by Syk on LAT and the associated scaffolding protein SLP-76 (Src homology region 2 domain-containing leukocytes protein of 76 kDa).<sup>11</sup> Notably, SHP-1 is susceptible to reversible inhibition by physiological concentrations of hydrogen peroxide, via conversion of cysteine sulfhydryl groups to sulfenic acid groups; reversible inactivation of tyrosine phosphatases by hydrogen peroxide is a common mechanism whereby generation of oxidants up-regulates tyrosine kinase signaling.<sup>15–20</sup>



Figure I Mast cell activation: environmental stimulants, membrane receptors, intracellular signaling pathways and degranulation.

**Notes:** (**A**) Allergens, IgE antibodies and the FcεRI receptor. Interactions of antigenic allergens with IgE antibodies create acomplex that activates FcεRI receptor on the mast cell membrane. These initiate intracellular signaling pathways that result in the release of pro-inflammatory mediators and cytokines. (**B**) Nutraceuticals and their mode of action. The compound 3-O-Me-EGCG down-regulated the cell surface expression of FcεRI, thus inducing mast cell stabilization. Biotin, berberine, H<sub>2</sub>S, PCB, lipoic acid and NAC, taurine, are agents that were found to have the clinical potential of allergy control by down-regulating these pathways. (**C**) Intracellular mediators and pathways. The mechanisms by which these agents may down-regulate pro-inflammatory activity are illustrated. Black arrows represent the up-regulation of pathways that were initiated by FcεRI interaction with antigen-IgE complex. Green arrows up-regulate and red arrows down-regulate, both act as anti-inflammatory by suppressing the black arrows pathways. In the signaling pathway following FcεRI activation, Syk acts as acentral hub. Berberine/H<sub>2</sub>Scan boost AMPK activity leading to Syk suppression, and SHP-1 opposes Syk activity as well. Yet, following Syk activation, ROS reversibly inhibitsSHP-1. Biotin can boost cGMP levels, which enhances the activity of SHP-1. NAC/taurine can boost endogenous production of H<sub>2</sub>S, which up-regulates cGMP and stimulates Nrf2's transcriptional activity. Nrf2 promotes induction down the suppresses ROS and promotes cGMP production. Lipoic acid increases Nrf2 expression, and PC-γ, p38, JNK, JIXK and NADPH oxidase. The combination of these pathways promotes mast cell degranulation, while ramping up gene transcription and boosting synthesis of pro-inflammatory cytokines and lipid mediators. Created with BioRender.com.

Antigen activation of FccRI in mast cells has been shown to rapidly induce production of superoxide in the extracellular space.<sup>8</sup> This effect is inhibited by wortmannin, diphenyleneiodonium, and apocynin – and hence points to membrane-bound NADPH oxidase as the superoxide source. Other research has determined that NOX2 is the predominant form of NADPH oxidase in mast cells.<sup>21,22</sup> Its activation may reflect PLC $\gamma$ -mediated production of diacylglycerol (which in turn promotes PKC activity), and PI3K-mediated activation of Rac, likely via Bruton's tyrosine kinase (BTK).<sup>6,23,24</sup> Importantly, inhibition of this initial burst of superoxide production suppresses antigen-stimulated mast cell degranulation.<sup>8</sup> A likely explanation is that hydrogen peroxide generated near the plasma membrane inhibits SHP-1 activity, thereby up-regulating Syk-mediated tyrosine phosphorylation of the FɛcRI signaling complex. Several studies show that heme oxygenase-1 (HO-1) induction in mast cells opposes mast cell degranulation and activation; this may reflect, in part, the fact that the bilirubin generated by HO-1 functions as an inhibitor of NOX2-dependent NADPH oxidase activity.<sup>25–32</sup>

# AMPK, Cyclic GMP, and Hydrogen Sulfide Down-Regulate Mast Cell Degranulation

Several molecular mechanisms have been shown to inhibit antigen-stimulated mast cell degranulation. These include activation of AMP-activated kinase (AMPK),<sup>14,33–36</sup> elevation of cyclic GMP (cGMP),<sup>37–39</sup> and increased generation of hydrogen sulfide (H<sub>2</sub>S).<sup>40–43</sup> With respect to AMPK, this has been shown to suppress the association of Lyn and Syk with the FccRI receptor complex.<sup>44</sup> While the basis of this effect has not yet been clarified, activated AMPK has been shown to confer a phosphorylation on the beta chain of this receptor; conceivably, this might suppress Lyn's ability to bind to this chain.<sup>44</sup>

With regard to cGMP, the cGMP-dependent protein kinase G II (PKGII) can confer an activating phosphorylation on the C-terminal region of SHP-1.<sup>45</sup> Whether the inhibitory impact of cGMP on mast cell degranulation reflects, in whole or in part, increased SHP-1 activity, requires further evaluation. The inhibitory effect of HO-1 activity on mast cell degranulation likely stems in part from the ability of carbon monoxide to promote cGMP production by soluble guanylate cyclase (sGC).<sup>46,47</sup>

Endogenous generation of H<sub>2</sub>S, as well as exposure to H<sub>2</sub>S-releasing drugs, have been shown to suppress mast cell degranulation.<sup>40–43</sup> Several complementary mechanisms may contribute to this effect. In at least certain contexts, H<sub>2</sub>S is capable of stimulating AMPK activity, via activation of calcium/calmodulin-dependent kinase kinase- $\beta$ .<sup>48–51</sup> H<sub>2</sub>S, via S-sulfhydrations of Keap1 that blocks its binding to Nrf2 and thereby stimulate Nrf2's transcriptional activity, promotes induction of HO-1.<sup>52–55</sup> And H<sub>2</sub> S can also promote cGMP generation by reversing

oxidative inhibition of sGC, as well as by inhibiting phosphodiesterase 5 (PDE5), which degrades cGMP in mast cells.<sup>56–58</sup> In regard to the latter mechanism, the drug inhibitor of PDE5, vardenafil, has been reported to oppose mast cell degranulation.<sup>39</sup>

# Discussion on Nutraceutical Strategies for Mast Cell Stabilization

The foregoing considerations offer a basis for proposing nutraceutical measures that could be expected to stabilize mast cells and thereby aid prevention and control of allergic reactions.

Berberine, a compound derived from certain medicinal herbs used in traditional Chinese medicine, is currently widely used in China both for glycemic control in type 2 diabetes, and as a hypolipidemic agent.<sup>59–61</sup> Its clinical utility in diabetes has been traced to its ability to activate AMPK<sup>62,63</sup> – in that respect, its mechanism of action appears to be comparable to that of the drug metformin (which itself is a modification of herbal compounds with hypoglycemic activity). Berberine, in vitro, has been found to inhibit mast cell degranulation by suppressing Syk phosphorylation – precisely as would be predicted for an AMPK activator.<sup>64,65</sup> In rodents, it has conferred protection in models of ovalbumin- or house-mite-induced allergic rhinitis, and in passive cutaneous anaphylaxis.<sup>65–67</sup>

Phase 2 inducing agents, via Nrf2-mediated induction of HO-1, could be expected to inhibit mast cell NADPH oxidase activity, as well as to boost cGMP via carbon monoxide generation. Lipoic acid and sulforaphane evolved from broccoli sprout extract (BSE) are phase 2 inducers with documented clinical utility.<sup>68–72</sup> Lipoic acid has been found to be protective in rodent models of anaphylaxis, lessening histamine release,<sup>73-75</sup> In a controlled clinical trial, ingestion of BSE was shown to benefit allergic rhinitis symptoms; another clinical study concluded that BSE ameliorated the nasal allergic response to inhalation of diesel exhaust particles.<sup>76,77</sup> Melatonin can promote phase 2 induction by increasing Nrf2 expression; also, via induction of Sirt1, it can boost AMPK activity while antagonizing the NF-kappaB-mediated phase of mast cell activation.78-80 It has shown efficacy in ovalbumin-induced allergic rhinitis in rats, and has been found to suppress mast cell degranulation provoked by water avoidance stress.<sup>81,82</sup> It also lessens inflammatory cytokine production by mast cells activated with phorbol ester and calcium ionophore, owing to downregulation of NF-kappaB signaling.83

While this discussion focuses on strategies for suppressing FceRI-mediated mast cell activation, it is of interest to note recent evidence that Nrf2 activation can also inhibit the MRFPRX2 signaling that mediates pseudo-allergic mast cell activation.<sup>84</sup> Another agent with the potential for inhibiting both FceRI and MRFPRX2 signaling in mast cells is paeoniflorin, a bioactive component in peony flower extracts; the mast cell stabilizing action of this agent has been demonstrated both in mast cell cultures and in rodent allergy models.<sup>85–88</sup> The direct molecular target of its action in this regard has yet to be defined.

Phycocyanobilin (PCB), a light-absorbing chromophore found in cyanobacteria (such as the food spirulina) and certain blue-green algae, is reduced within cells by biliverdin reductase to phycocaynorubin, a compound almost identical in secondary and tertiary structure to bilirubin.<sup>89,90</sup> Not surprisingly, PCB has been shown to mimic bilirubin's inhibitory effect on NADPH oxidase complexes - a phenomenon, which may be largely responsible for the profound antioxidant and anti-inflammatory activities of orally administered spirulina (or of its protein phycocyanin, to which PCB is covalently bound) in a wide range of rodent models of health disorders.<sup>90–93</sup> Indeed, oral administration of spirulina or phycocyanin has been found to alleviate symptoms and reduce histamine release in rat models of anaphylaxis induced by ovalbumin or compound 48/80; spirulina also stabilized mast cells and lessened symptoms in ovalbumin-induced allergic rhinitis.94-97 Small clinical trials with modest oral doses of spirulina have found it to confer symptomatic benefits in allergic rhinitis, and oral spirulina has also been shown to decrease interleukin-4 production by peripheral blood mononuclear cells stimulated ex vivo.<sup>98-100</sup> The latter suggests that, independent of its impact on mast cells, spirulina might lessen the propensity to generate IgE.

In supraphysiological concentrations, which are achievable with practical and well-tolerated high-dose supplementation, the B vitamin biotin can directly activate sGC – mimicking the physiological effects of nitric oxide and carbon monoxide in that regard.<sup>101–103</sup> However, it is incapable of increasing sGC's activity by more than 2–3-fold – explaining why it cannot produce profound hypotension the way that NO overdoses can. The authors are unaware of any past effort to evaluate the impact of supraphysiological biotin concentrations on mast cell activation.

Endogenous production of  $H_2S$  can be boosted by supplemental N-acetylcysteine (NAC), as cysteine is the preferred substrate for generation of  $H_2S$  by cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE).<sup>104–107</sup> In addition, by promoting increased glutathione synthesis, NAC might help to counter the inhibitory effect of oxidants on SHP-1 activity, as glutathione acts to reverse the oxidative inhibition of this enzyme.<sup>17,108,109</sup> In vascular tissues, supplemental taurine has recently been found to induce expression of both CBS and CSE.<sup>105,110,111</sup> It is not clear whether taurine can have this effect in mast cells. However, taurine administration has been found to alleviate ovalbumin-induced allergic rhinitis in mice.<sup>112,113</sup>

A further resource for mast cell stabilization is offered by benifuuki tea, a cultivar of green tea that is unusually rich in an O-methylated form of the prominent green tea catechin epigallocatechin-gallate (EGCG); the site of methylation is on the 3"-hydroxyl of the gallate group.<sup>114</sup> This type of tea has been shown to be clinically effective in seasonal allergies (Japanese cedar pollinosis), and its efficacy is thought to reflect the fact that O-methylated EGCG has far superior pharmacokinetics compared to EGCG per se.<sup>115-118</sup> Both EGCG and O-methylated EGCG can stabilize mast cells in vitro, and this effect appears to be mediated through the high-affinity binding of these compounds to the 67 kDa laminin receptor (67LR) on mast cells.<sup>114,119–126</sup> How this receptor induces mast cell stabilization is at present poorly understood, although the interaction of EGCG with the laminin receptor is associated with down-regulated cell surface expression of FceRI.<sup>124</sup> This effect is homologous to the ability of EGCG/67LR interaction to down-regulate the surface expression of epidermal growth factor receptors in cancer cells, an effect reflecting accelerated internalization of these receptors; perhaps EGCG likewise induces endosomal uptake of FccRI.<sup>127</sup> Interaction of EGCG with 67LR also inhibits mast cell degranulation induced by calcium ionophores, blocking phosphorylation of myosin II regulatory light chain.<sup>125</sup> And EGCG-mediated inhibition of NADPH oxidase assembly in stimulated mast cells has been reported.<sup>122</sup> The clinical practicality of using 3-O-methyl EGCG to manage allergies would evidently be greater if polyphenol extracts of benifuuki tea were commercially available.

#### Conclusions

In summary, it can be concluded that nutraceutical regimens providing some or all of the following agents – berberine, spirulina (or isolated PCB), lipoic acid (and/or broccoli sprouts), melatonin, NAC, taurine, high-dose biotin, benifuuki catechins – may have clinical potential for

| Nutraceuticals                                     | Dosage                                   |
|----------------------------------------------------|------------------------------------------|
| Spirulina                                          | 5–15 g daily (or 30–100 mg<br>PCG daily) |
| Lipoic acid                                        | 600 mg, 2–3 times daily                  |
| Broccoli Sprout Extract (Avmacol <sup>TM</sup> )   | 375 mg twice daily                       |
| Berberine                                          | 500 mg twice daily                       |
| Biotin                                             | 10–20 mg, twice daily                    |
| N-Acetylcysteine                                   | 600 mg, 2–3 times daily                  |
| Taurine                                            | 2–3 g daily                              |
| Catechin-enriched Green Tea<br>Extract (Benifuuki) | 500 mg, twice daily                      |

| Table                                          | L | Suggested | Dose | Schedules | for | Nutraceuticals | with |  |
|------------------------------------------------|---|-----------|------|-----------|-----|----------------|------|--|
| Potential for Opposing Mast Cell Degranulation |   |           |      |           |     |                |      |  |

mast cell stabilization and allergy control. The mechanisms whereby these agents may down-regulate FccRI signaling are depicted in Figure 1. It would be of interest to study regimens of this sort in rodent models of allergy. It seems likely that a number of small effects that have a complementary impact could result in a substantial clinical benefit.

Table 1 suggests dose schedules of the various discussed nutraceuticals that might be expected to have some clinical impact. We do not represent these dose schedules as ideal for allergy management – rather, these are dose schedules that have shown clinical impact in other contexts, and hence might have potential to be active in allergy.

# **Abbreviations**

SyK, spleen tyrosine kinase;  $H_2S$ , Hydrogen sulfide; PCB, Phycocyanobilin; LAT, linker for activated T cells; PI3K, phosphatidylinositol-3-kinase; SHP-1, Src homology region 2 domain-containing phosphatase 1; BTK, Bruton's tyrosine kinase; HO-1, heme oxygenase-1; AMPK, AMP-activated kinase; cGMP, cyclic GMP; PKGII-cGMP, dependent protein kinase G II; sGC, soluble guanylate cyclase; PDE5, phosphodiesterase 5; BSE, broccoli sprout extract; NAC, N-acetylcysteine; CBS, cystathionine  $\beta$ -synthase; CSE, cystathionine  $\gamma$ -lyase; ROS, reactive oxygen species.

# **Author Contributions**

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval for the version to be published; and agreed to be accountable for all aspects of the work.

# Disclosure

Author MFM is co-inventor and co-owner of a patent covering nutraceutical uses of phycocyanobilin oligopeptides derived from spirulina. Author JJD is Director of Scientific Affairs for Advanced Ingredients for Dietary Products. The authors have no other conflicts of interest to disclose.

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