Mast cell stabilisers

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ABSTRACT

Mast cells play a critical role in type 1 hypersensitivity reactions. Indeed, mast cell mediators are implicated in many different conditions including allergic rhinitis, conjunctivitis, asthma, psoriasis, mastocytosis and the progression of many different cancers. Thus, there is intense interest in the development of agents which prevent mast cell mediator release or which inhibit the actions of such mediators once released into the environment of the cell. Much progress into the design of new agents has been made since the initial discovery of the mast cell stabilising properties of khellin from *Ammi visnaga* and the clinical approval of cromolyn sodium. This review critically examines the progress that has been made in the intervening years from the design of new agents that target a specific signalling event in the mast cell degranulation pathway to those agents which have been developed where the precise mechanism of action remains elusive. Particular emphasis is also placed on clinically used drugs for other indications that stabilise mast cells and how this additional action may be harnessed for their clinical use in disease processes where mast cells are implicated.

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1. Introduction

Mast cells were first described by Paul Ehrlich in 1878, who named them "*mastzellen*", meaning "feeding cells" because of their appearance (Ehrlich, 1878; Galli et al., 1999). The precursors to mast cells, CD34$^+$ progenitor cells, are formed in the bone marrow during haematopoiesis and circulate into the bloodstream (Robbie-Ryan and Brown, 2002). These haematopoietic progenitor cells remain undifferentiated in the blood and become differentiated only upon entering the tissue, where they become mature mast cells under the influence of local factors. Mast cells can be very long lived, ranging from weeks to months (Wedemeyer et al., 2000). They are found in almost all parts of the body along with the endothelial cells of the blood vessel wall as well as the mucosal epithelial tissue (Nauta et al., 2008). It has been established by many studies that mast cell proliferation, differentiation and survival are strictly regulated by stem cell factor (SCF), which act through its Kit receptor expressed on the mast cell surface (Sundström et al., 2001). Under normal conditions, mast cell numbers in tissue are considered to be relatively constant, except when mast cell hyperplasia is established in different pathologies such as chronic inflammatory processes, fibrotic disorders and wound healing (Bischoff and Sellge, 2002).

Two distinct phenotypes of mast cells are distinguishable based on the types of proteases contained in their exocytotic granules. Mucosal mast cells contain only tryptase (namely M_T), and are mainly found in the mucosa of the gastrointestinal system and in the lamina of the respiratory tract, whereas the mast cells of connective tissue contain tryptase, chymase, cathepsin G and carboxypeptidase (namely M_{TC}), and which are localised in the sub mucosa of the gastrointestinal tract, skin and peritoneum (Rao, 2002a; Puxeddu et al., 2005).

1.1. Mast cell activation

Mast cells express a vast array of stimulatory and inhibitory receptors. Mast cell activation can be induced by both immunologic (immunoglobulin E (IgE)) and non immunologic substances. Crosslinking of IgE, immunoglobulin G_1(IgG$_1$), immunoglobulin G_{2a} (IgG$_{2a}$) and immunoglobulin G_{2b} (IgG$_{2b}$) antibodies on the high affinity IgE receptor (FcεRI), the FcγRI (human), FcγRIIa (mouse and human) or FcγRIII (mouse) receptor by allergen incites antigen specific mast cell activation (Nimmerjahn and Ravetch, 2008).

1.1.1. Mechanism of IgE mediated degranulation: The classic pathway

IgE dependant activation of mast cells, basophils, monocytes, and macrophages plays a vital role in the pathogenesis of allergic

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reactions (Maurer et al., 1994; Sutton et al., 2000; Owen, 2007). IgE is the major antibody in allergic diseases. The main physiological role of IgE is believed to be to protect the external mucosal surface of the body by the local recruitment of plasma factors and effector cells, by inducing an acute inflammatory reaction (Rao, 2002b). IgE is largely cell bound, especially to mast cells. Mast cell degranulation results from antigen crosslinking of IgE on cell surface receptors.

1.1.2. Steps involved in FcεRI signal transduction leading to mast cell degranulation

An enzyme of the Src family of tyrosine kinases, called Lyn (Lck/ Yes novel tyrosine kinase), is constitutively associated with the β chain of the FcεRI. Upon crosslinking of IgE bound to the α subunits of FcεRI, Lyn phosphorylates a special amino acid sequence called ITAM (immunoreceptor tyrosine based activation motif) that is located on both β and γ chains of FcεRI. Phosphorylation of the β chain recruits more Lyn, which can associate by its SH2 domain (Src homology domain 2), a region of the Src family protein that binds phosphorylated tyrosine containing sequences. Through this mechanism the signal transduction is magnified. Phosphorylation of the γ chain provides a binding site for the cytoplasmic tyrosine kinase, Syk (spleen tyrosine kinase), which upon phosphorylation by Lyn, and possibly through autophosphorylation, becomes activated. Inhibitory signals to these processes are also present, in the form of signal regulatory proteins (SIRPs), which cause downregulation through catalysis of dephosphorylation reactions. Activated Syk phosphorylates kinases including PI_3 (phosphoinositol-3-OH-kinase), which results in generation of PIP_3 (phosphatidylinositol [3,4,5] triphosphate), and its association with another tyrosine kinase, Btk (Bruton's tyrosine kinase) allows association of Btk with the plasma membrane. Other enzymes thought to be important following Syk activation include MAP kinase (mitogen activated protein kinase), protein kinase C and Phospholipase C γ (PLC γ). Upon Btk activation, PLC γ is phosphorylated by Syk and generates inositol trisphosphate (IP_3) which causes Ca^{2+} release from the endoplasmic reticulum (ER). Depletion of intracellular Ca^{2+} stores activates store operated calcium channels (SOCC) and allows Ca^{2+} influx. This is aided by increased membrane fluidity through methylation of phospholipids. Ca^{2+} influx promotes activity within the cytoskeleton, causing microtubule assembly and contraction of microfilaments. Disassembly of actin myosin complexes facilitates granule contact with the cell membrane. FcεRI activation also results in a rise in cyclic adenosine monophosphate (cAMP), which mediates phosphorylation of the granule membrane proteins, altering their permeability. Swelling of the granules aids fusion of granule and plasma membranes, followed by release of granule contents (Turner and Kinet, 1999).

However, the classical pathway does not explain all allergic responses. For example, active systemic anaphylaxis developed in mice that were deficient in mast cells, IgE, or FcεRIα chain (Strait et al., 2002). Various studies have demonstrated the existence of other major distinct pathways resulting in allergen triggered systemic anaphylaxis, which are mediated by basophils, IgG, IgG receptor, and platelet activating factor (PAF) (Tsujimura et al., 2008). It has been demonstrated that mast cells can also be activated by neuropeptides released by neuronal stimulation during stress, which include corticotrophin releasing factor (CRF), urocortin (Ucn), nerve growth factor (NGF), substance P (SP) and neurotensin (NT) (Suzuki et al., 1999; Theoharides et al., 2004c). Activated mast cells secrete vasoactive, proinflammatory and neurosensitizing molecules which interact with keratinocytes, endothelial cells or nerve endings, resulting in chronic inflammation and neuropathic hypersensitivity or pain. It has been shown that such mast cell activations can either be mediated through specific receptors (i.e. NK_1 receptors), or by activating G protein directly, which is receptor independent (Theoharides and Cochrane, 2004a). Several agents such as opioids and physical stimuli also activate mast cells and they do this independently of IgE (Machado et al., 1996). Moreover, Der p 1 (a major house dust mite allergen) and bee venom phospholipase A2 (a major allergen in bee sting allergy), have been shown to induce mast cell activation independently of the classical pathway. Interestingly, studies showed that certain stimulators could induce biological mediator release e.g. histamine, interleukin 4 (IL4) and tumour necrosis factor alpha (TNFα) from unsensitised mast cells in the absence of detectable changes in intracellular Ca^{2+} such as TSL1 antigens from *Trichinella spiralis* muscle larvae (Arizmendi-Puga et al., 2006).

2. Sources of mast cell stabilisers (Fig. 1)

As with the discovery of many medicines in clinical use today, natural resources have served as a very fruitful source of mast cell stabilisers. Invariably, preparation of semisynthetic derivatives of the natural "hits" from screening assays resulted in the generation of more potent derivatives. Purely synthetic compounds have been prepared to target specific enzymes or receptors involved in degranulation. Oftentimes, these compounds were designed to target other conditions but as a consequence of their action they have the knockon effect of also stabilising mast cells. Promising results have
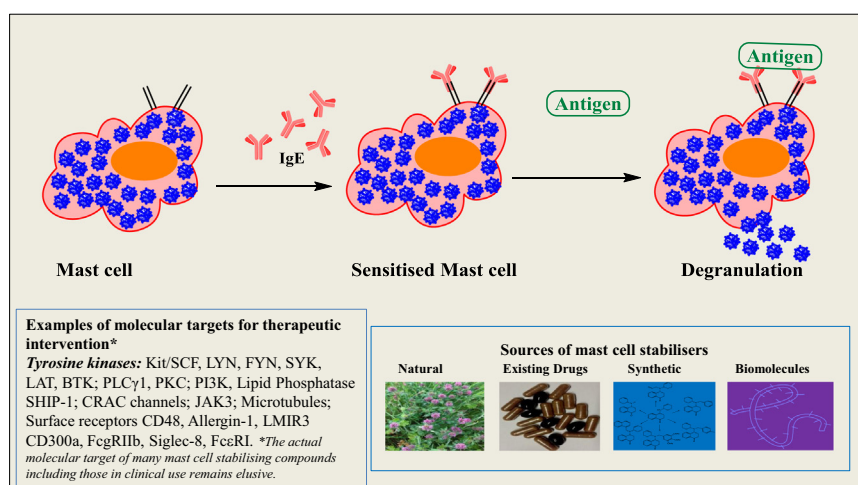

Fig. 1. Mast cell sensitisation, degranulation, possible molecular targets for therapeutic intervention and sources of mast cell stabilisers.