J. Pharm. Pharmacol. 1990, 42: 457–461
Received January 15, 1990

© 1990 J. Pharm. Pharmacol.

Review

Mast Cell Degranulating Peptide: A Multi-functional Neurotoxin

M. REZA ZIAI, SHELLEY RUSSEK, HSUEI-CHIN WANG, BERNARD BEER AND ARTHUR J. BLUME

CNS Research Department, Medical Research Division, American Cyanamid Company, Pearl River, New York 10965, USA

Abstract—This review discusses our present knowledge of the structure and activities of the mast cell degranulating peptide (MCDP). This peptide is a basic, 22 amino acid residue component of honey bee venom with striking immunological and pharmacological activities. MCDP is a potent anti-inflammatory agent, but at low concentrations it is a strong mediator of mast cell degranulation and histamine release. MCDP is also an epileptogenic neurotoxin, an avid blocker of the potassium channels and can cause a significant lowering of the blood pressure in rats. Some of the biological activities of MCDP appear to have distinct mechanisms and may represent a good illustration of the structure-function relationship.

The venom of the European honey bee (*Apis mellifera*) has long been considered to be a rich source of anti-inflammatory activities. Even in modern times, "apitherapy" has continued to be a common practice in China, Eastern Europe and South America for a variety of inflammations and infections (Beck 1935; Somerfield 1984; Hider 1988). Although bee venom has not quite lived up to its reputation as the panacea of folk medicine, its striking immunological and anti-allergic activities have been repeatedly examined and verified by several laboratories and clinics around the world (Lorenzetti & Fortenberry 1972; Zurier et al 1973; Chang & Bliven 1979; Bosquote et al 1988; Hadjipetrou-Kourounakis & Yiangou 1988).

Bee venom contains several proteins, peptides, physiologically active amines, sugars, phospholipids, amino acids, pheromones and other volatile substances. Almost 50% of its peptide fraction consists of melittin, a surface active, highly cytolytic peptide of 26 amino acids which occurs in a tetrameric form with a relative molecular weight (Mr) of 12 kilodalton (Nakajima et al 1985; Hider 1988). Melittin is devoid of any known anti-inflammatory properties but can mediate the release of histamine from mast cells, mostly by a general lytic process (Zurier et al 1973; Hanson et al 1974; Jasani et al 1979).

Another well known peptide component of the bee venom is apamin. This 18 amino acid peptide is a potent convulsant neurotoxin capable of blocking neuronal Ca^{2+}-activated potassium (K) channels (Romey & Lazdunski 1984). No significant effects by apamin on the immune system have yet been demonstrated (Zurier et al 1973).

Almost all of the immunological activities of the peptide fraction of bee venom have been attributed to a single peptide: mast cell degranulating peptide (MCDP), also known as peptide 401 (Billingham et al 1973; Banks et al 1976). MCDP, which constitutes 1–2% of the bee venom is a highly cationic 22 amino acid peptide (Mr; 2·5 kilodalton) containing two arginine, five lysine and five strongly hydrophobic amino acid residues and an amidated C-terminus (Fig. 1).

Correspondence to: M. R. Ziai, CNS Research Department, American Cyanamid Company, Pearl River, NY 10965, USA.

Due to the absence of free carboxyl groups and the abundance of basic amino acids, MCDP has an isoelectric point of 12. It has been purified to homogeneity, completely sequenced and was shown to be rich in α-helical structure (Breithaupt & Habermann 1968; Gauldie et al 1976; Bidard et al 1987). Its predicted three dimensional architecture, however, is almost spherical with eight positive centres evenly distributed over its molecular surface (Hider & Ragnarsson 1981; Kumar et al 1988). This peptide contains four cysteine residues allowing the formation of two intramolecular disulphide bonds between the positions 3–15 and 5–19, resulting in a tightly packed, cyclic structure of two asymmetric loops (Gauldie et al 1978; Argiolas et al 1985; Bidard et al 1987). Although the amino acid sequence, arrangement of the disulphide bonds and the three dimensional structure of MCDP is similar to that of apamin (they are commonly referred to as isotoxins), they have distinct cellular receptors and elicit completely different physiological responses (Gauldie et al 1978; Hider & Ragnarsson 1981;

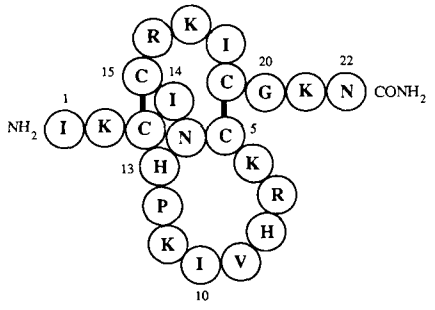

FIG. 1. Primary structure of the bee venom mast cells degranulating peptide (MCDP). The relative position of the amino acids is a schematic depiction of the two asymmetric, overlapping and tightly packed peptide loops formed by the presence of two disulphide bonds (black bars) in the MCDP molecule. Amino acid symbols are; I, isoleucine; K, lysine; C, cysteine; N, asparagine; R, arginine; H, histidine; V, valine; P, proline; and G, glycine.

Table 1. Various biological activities of the mast cell degranulating peptide (MCDP).

Target	Activity
Immune system	1. Anti-inflammatory 2. Histamine releasing
Central nervous system	1. Convulsive 2. Blocking of K-channels
Cardiovascular system	Anti-hypertensive

Romey & Lazdunski 1984; Bidard et al 1987; Hider 1988; Kumar et al 1988).

MCDP has two potent but antagonistic immunological activities. It is a powerful anti-inflammatory agent, but at low concentrations mediates the degranulation of mast cells thus evoking an inflammatory response.

In addition, MCDP has two important pharmacological properties, one in the central nervous system (CNS), where MCDP acts as a neurotoxin capable of blocking a class of voltage-gated potassium channels (Taylor et al 1984; Nakajima et al 1985; Bidard et al 1987; Cherubini et al 1987, 1988). The second is a cardiovascular effect. In experiments with rats, MCDP has proved to be a potent hypotensive agent, significantly lowering blood pressure (Breithaupt & Habermann 1968; Hanson et al 1974; Buku et al 1989). Since little information is available on the latter action of MCDP, it will not be discussed further in this review. The major biological activities of MCDP are summarized in Table 1.

Anti-inflammatory Activity of MCDP

Inflammation is a complex process through which the body repairs tissue injury and counters infections. The most common disease of chronic inflammation in man is rheumatoid arthritis. Traditionally, the experimental adjuvant-induced arthritis in rats has been widely accepted as a suitable animal model resembling the human disease and has served as a useful system for testing various anti-inflammatory agents. Adjuvant-arthritis is a general cell-mediated polyarthritis which can be induced in rats within 10–12 days following the injection of the heat-killed *Mycobacterium tuberculosis* in Freund's adjuvant (Banks et al 1976). Utilizing this model Billingham et al (1973) demonstrated that MCDP markedly suppressed the development of adjuvant arthritis and effectively reduced the progression of primary and secondary lesions in the established disease. The anti-inflammatory activity of MCDP was 2–100 times more potent than comparable doses of hydrocortisone, mepyramine, indomethacin, phenylbutazone, sodium salicylate or dexamethasone, agents commonly used to alleviate the severity of rheumatoid arthritis in man (Billingham et al 1973; Hanson et al 1974; Somerfield 1984). Other tests of the anti-inflammatory drug action such as rat paw oedema test, plasma protein accumulation or the effect of histamine on cultured human skin, have also indicated that MCDP is almost 100 fold more potent than hydrocortisone and several other anti-inflammatory drugs examined (Billingham et al 1973; Hanson et al 1974; Banks et al 1976). In animal studies, MCDP administered intravenously, immediately before an intradermal injection of an inflammatory agent, could prevent extravasation (the escape of fluid into the surrounding tissue) at a dose of 200 mg kg^{-1} body weight. However, it was much less effective if given intradermally following the injection of the irritant. This has been thought to be due to the slow spread of the peptide from the site of injection (Hanson et al 1974; Banks et al 1976). Furthermore, pretreatment of the animals with antagonists of histamine and 5-hydroxytryptamine could inhibit the inflammatory actions of MCDP but did not diminish the activity of MCDP against other inflammatory agents (Hanson et al 1974).

The mechanism of MCDP action is still obscure. Originally it was thought that MCDP, like the whole bee venom, exerts its anti-inflammatory activities by stimulation of the adrenal gland to release corticosteroids (Lorenzetti & Fortenberry 1972; Moczydlowski et al 1988). This hypothesis however, has been repeatedly questioned, since in several other studies, adrenalectomized rats showed an identical response to MCDP as their sham operated counterparts. Furthermore, MCDP consistently failed to mediate the release of corticosterone from suspensions of adrenal cortical cells in culture (Billingham et al 1973; Hanson et al 1974; Banks et al 1976). The anti-inflammatory action of MCDP is apparently unaffected by regional denervation, nor is it likely to be due to a reduction in tissue perfusion (Hanson et al 1974).

A possible mode of MCDP action was proposed following the observation that MCDP binds exclusively and specifically to white blood cells, and it is a strong in-vitro inhibitor of the conversion of arachidonic acid into prostaglandin E_2 (Banks et al 1976; Hider 1988). Prostaglandin E_2 is actively involved in the inflammatory process and causes vasodilation, potentiates the permeability effects of histamine or bradykinin and enhances the sensitivity to pain (hyperalgesia). Therefore, an inhibitor of the cyclo-oxygenase pathway, through which arachidonic acid is converted to prostaglandins, would be expected to reduce the severity of the early phases of the inflammatory reaction. Aspirin is a familiar example of such an inhibitor. It must be strongly emphasized, however, that to the best of the authors' knowledge, solid pharmacological data indicating the existence, type or affinity of specific MCDP receptors on white blood cells are presently unavailable.

The most recent hypothesis regarding the anti-inflammatory mode of MCDP action suggests that the peptide acts through an open tetravalent mercaptoid form (Buku et al 1989). At high concentrations, the MCDP molecule occupies the disulphide hinge regions of the two IgE molecules cross-linked by the antigen (allergen), resulting in changes in their conformation. This in turn may distort the normal configuration of the IgE-Fc receptor complex which is necessary for successful signal processing, activation and degranulation of mast cells.

Although the precise mechanism of MCDP action must await further studies, it is conceivable that this peptide exerts its anti-inflammatory effects through multiple pathways and all modes of action thus far suggested (and perhaps more) are operative at once. However, all these proposals must, for the present, remain largely speculative.

Mast Cell Degranulation by MCDP

A second feature of the MCDP, radically antagonistic to its anti-inflammatory activities, is its ability to degranulate mast

cells and release histamine. The granules of a number of mast cell sub-types contain several active agents (e.g. histamine), a host of chemotactic and activating factors, and various hydrolytic enzymes. When a mast cell releases its granular contents into the extracellular space ("degranulates"), it mediates the early phases of an inflammatory response. This involves vasodilation, increased vascular permeability and chemotaxis. Degranulation of mast cells is a multi-step and complex process which has not been totally elucidated. Taking a simplified view, it starts with the binding of antigen to IgE molecules. This is a bivalent reaction which results in cross linking of two IgE molecules on the plasma membrane of mast cell. This causes dimerization of the IgE receptors which then triggers a series of events, starting with the activation of phospholipase C, through mobilization of calcium ions, protein phosphorylation, activation of phospholipase A_2, leading to the formation of lysolecithin. The latter then mediates the fusion of mast cell granules with its plasma membrane and causes the release of chemical mediators.

A number of small peptides have been identified as strong mediators of histamine release and MCDP is certainly one such peptide. In-vitro studies using highly purified synthetic MCDP, have shown that this peptide can liberate 50% of the histamine content of rat peritoneal mast cells at a concentration range of 10^{-8}–10^{-7} M (Jasani et al 1979; Gushchin et al 1981; Chhatwal et al 1982; Buku et al 1989). MCDP is a more potent histamine liberator than several other known histamine releasers such as concanavalin A (Chhatwal et al 1982), protamine, bradykinin, tuftsin, ACTH and melittin (Jasani et al 1979). The histamine releasing ability of MCDP is equivalent to compound 48/80, a remarkably potent low molecular weight synthetic liberator of histamine (Hanson et al 1974; Banks et al 1976; Chhatwal et al 1982).

Again, the exact mechanism of MCDP action in releasing histamine is unclear. In fact, the whole subject of the mode of action of histamine liberators is complex and controversial. However, this peptide possesses adequate structural features to be a histamine liberator. It is a highly cationic peptide with amidated carboxyl terminal and lacks acidic side chains, features apparently necessary for a peptide to be an effective histamine liberator (Jasani et al 1979).

Activation of mast cells involves increased permeability of the plasma membrane to Ca^{2+} ions. This in turn results in protein phosphorylation and swelling of the granules before fusion to the plasma membrane. The highly basic MCDP may directly interact with the acidic side groups of the calcium channels and cause their activation (Buku et al 1989). This would open the calcium channels, cause a rise in the intracellular Ca^{2+} concentration and could result in mast cell degranulation. Alternatively, MCDP, like many other basic histamine liberating peptides, may be able to mimic a particular amino acid sequence within the Fc region of IgE, thus directly reacting with the IgE receptors of mast cells causing degranulation (Jasani et al 1979; Buku et al 1989).

Blocking of the Potassium Channels by MCDP

In addition to the two major properties described above, MCDP also possesses a potent CNS activity. This peptide is an epileptogenic neurotoxin capable of blocking voltage-gated potassium (K) channels. These channels are integral membrane proteins of great diversity present in practically all mammalian cells. In excitable cells, some K-channels in association with sodium channels, are responsible for the generation of the action potentials, the release of neurotransmitters and, reportedly, the process of learning and memory. In addition, K-channels perform important functions in the immune and endocrine systems, regulation of blood pressure and chemosensory functions such as taste (reviewed by Jan & Jan 1989).

A number of snake, scorpion and bee venom-derived peptides, including MCDP, have been shown to interact with the voltage-gated or calcium activated K-channels. MCDP has high affinity receptors throughout the brain, kidney, adrenal and intestine (Bidard et al 1987; Cherubini et al 1987, 1988). This peptide is known to be a potent blocker of at least one sub-type of K-channel, that responsible for the transient (or "A") type K-current (Stansfeld et al 1987; Gandolfo et al 1989a, b). MCDP efficiently inhibits binding of the snake venom-derived dendrotoxin I and β-bungarotoxin to this type of K-channel as determined by the conventional ligand binding assays and cross linking of these neurotoxins to their receptors in brain (Gauldie et al 1978; Stansfeld et al 1987; Schmidt & Betz 1989). The putative brain receptor for MCDP is a 77 kilodalton protein which is also a receptor for dendrotoxin I and β-bungarotoxin (Rehm & Lazdunski 1988; Schmidt & Betz 1989). Furthermore, drugs capable of activating K-channels prevent the epileptogenic actions of MCDP in rats when administered before the injection of MCDP. This finding furthers the evidence for specific interaction of this peptide with the neuronal K-channels (Gandolfo et al 1989a, b). Moreover, a recent report has shown that MCDP also appears to share the binding site with charybdotoxin, a neurotoxin originally described as a specific blocker of the calcium activated K-channel (Gimenez-Gallego et al 1988; Schweitz et al 1989). Interestingly, Cherubini et al (1987) have detected an endogenous brain peptide which is immunologically and functionally related to MCDP, raising the possibility that MCDP-like peptides in the brain may be important in the long term potentiation of synaptic transmission. This finding may also imply the existence of endogenous K-channel blocking and, perhaps, activating peptides in the brain.

The effect of MCDP on the immune system has not yet been attributed to its avidity for K-channels. However, K-channels are known to perform important functions in the immune system (reviewed by Lewis & Cahalan 1988), and it is conceivable that the interaction of MCDP with cells of the immune system may involve one or more types of voltage-gated K-channels. Specifically, since Ca^{2+} ions appear to be important factors in mast cell degranulation, it is possible that blocking of K-channels with MCDP would depolarize the plasma membrane of the mast cell, resulting in an enhanced influx of Ca^{2+} ions from the extracellular space into the cell. It must be noted, however, that unlike the calcium channels, the K-channels have not yet been directly detected in the plasma membranes of mast cells. With the availability of several synthetic, recombinant or highly purified neurotoxins, elucidating the functional roles of K-channels in the mast cells represents an exciting new area of

research in immunology where, traditionally, there have been parallels with the CNS.

Since MCDP has been long considered to have therapeutic potential and also because of its pronounced CNS activities, its toxicity has been studied to some degree. In comparison with its isotoxin, apamin, MCDP has a surprisingly low toxicity when administered outside of the CNS. However, when injected directly into the brain cavity of adult rats, MCDP causes epileptic seizures and death at approximately 0·3 nmol per animal (Taylor et al 1984; Gandolfo et al 1989a). Milligram quantities of MCDP have been intradermally or intravenously injected into mice with no lethality (Billingham et al 1973; Banks et al 1976). This may imply that MCDP, when injected systemically, is unable to cross the blood-brain barrier. Interestingly, apamin which is very similar in structure to and only four amino acids shorter than MCDP, appears to pass from blood to brain (Moczydlowski et al 1988). To the present time, the LD50 value for MCDP injected intravenously or subcutaneously in mice has not been determined. The toxicity induced by injecting massive doses of MCDP in rats, however, has been attributed to its histamine releasing activities (Banks et al 1978). Unfortunately, detailed toxicological studies on MCDP are presently unavailable.

Structure-function Relationship in MCDP

The structure-function relationship in MCDP has been the subject of several studies. There is strong evidence that the multi-functional nature of MCDP is a reflection of its unique amino acid backbone. The three dimensional structure of MCDP appears to be essential for its biological activities, since reduction and carboxymethylation of the two disulphide bonds (Fig. 1), abolishes all of its immunological and CNS activities (Banks et al 1978; Gushchin et al 1981). Irreversible modification of its two arginine residues does not affect the anti-inflammatory or histamine releasing actions of MCDP but causes a complete loss of its CNS activities (Banks et al 1978; Gushchin et al 1981; Taylor et al 1984). Dependent upon the type of the anti-inflammatory assays used, substitution of the two histidine residues either has no effect (Banks et al 1978), or significantly impairs the action of MCDP (Gushchin et al 1981). Modification of the ε-amino groups of the five lysine residues in MCDP results in a complete loss of its activities (Banks et al 1978; Gushchin et al 1981; Taylor et al 1984). It appears, therefore, that MCDP possesses multiple functional domains which are relatively distinct and occupy different sites on its molecule (Banks et al 1978). This conclusion however, must be drawn with caution since the available evidence does not indicate the existence of one distinct functional domain for each biological activity of MCDP.

The differential effects of chemical modifications on various biological activities of MCDP may imply that this peptide interacts with distinct receptors which are target cell-specific. It is not at all surprising that a bioactive peptide contains multiple effector domains. In several multi-functional polypeptides, distinct molecular domains appear to act relatively independently in performing the various biological effects of the parent protein. Immune interferon (IFN-γ) may be a suitable example, in which the functional domains responsible for the anti-proliferative, HLA antigen modulation and anti-viral actions are apparently distinct from those involved in the receptor binding and down regulation of the expression of cell surface antigens other than HLA (Ziai et al 1986).

The existence of distinct molecular domains on the MCDP molecule must await further studies by peptide chemists, pharmacologists and perhaps molecular biologists. Cloning and in-vitro mutagenesis of the gene encoding MCDP would be a powerful approach in defining the molecular profile of this interesting neurotoxin . With the increasing interest in the CNS activities of MCDP, the latter approach is likely to be pursued in the near future.

References

Argiolas, A., Herring, P., Pisano, J. J. (1985) Amino acid sequence of bumblebee MCD peptide: a new mast cell degranulating peptide from the venom of the bumblebee *Megabombus pennsylvanicus*. Peptides 6 (Suppl.3): 431–436

Banks, B. E. C., Rumjanek, F. D., Sinclair, N. M., Vernon, C. A. (1976) Possible therapeutic use of a peptide from bee venom. Bull. Inst. Pasteur 74: 137–144

Banks, B. E. C., Garman, A. J., Habermann, E. (1978) Structure-activity studies on apamin and mast cell degranulating peptide (MCDP)-401. J. Physiol. (London) 284: 160–161

Beck, B. (1935) Bee Venom Therapy, Appleton, New York

Bidard, J. N., Mourre, C., Lazdunski, M. (1987) Two potent central convulsant peptides, a bee venom toxin, the MCD peptide, and a snake venom toxin, dendrotoxin I, known to block K channels, have interacting receptor sites. Biochem. Biophys. Res. Commun. 143: 383–389

Billingham, M. E. J., Morley, J., Hanson, J., Shipolini, R. A., Vernon, C. A. (1973) An anti-inflammatory peptide from bee venom. Nature (London) 245: 163–164

Bosquote, J., Menardo, J.-L., Velasquez, G., Michel, F.B. (1988) Systemic reactions during maintenance immunotherapy with honey bee venom. Annal. Allergy 61: 63–68

Breithaupt, H., Habermann, E. (1968) Mastzelldegranulierendes peptid (MCD-peptid). Arch. Pharmak. Exp. Pathol. 261: 252–270

Buku, A., Blandina, P., Birr, C., Gazis, D. (1989) Solid phase synthesis and biological activity of mast cell degranulating (MCD) peptide: a component of bee venom. Int. J. Peptide Protein Res. 33: 86–93

Chang, Y.-H., Bliven, M. L. (1979) Anti-arthritic effect of bee venom. Agents Actions 9: 205–211

Cherubini, E., Ben-Ari, Y., Gho, M., Bidard, J.-N., Lazdunski, M. (1987) Long-term potentiation of synaptic transmission in the hippocampus induced by a bee venom peptide. Nature (London) 328: 70–73

Cherubini, E., Neuman, R., Rovira, C., Ben-Ari, Y. (1988) Epileptogenic properties of the mast cell degranulating peptide in CA3 hippocampal neurones. Brain Res. 445: 91–100

Chhatwal, G.S., Ahnert-Hilger, G., Beress, L., Habermann, E. (1982) Palytoxin both induces and inhibits the release of histamine from rat mast cells. Int. Archs. Allergy Appl. Immunol. 68: 97–100

Gandolfo, G., Gottesmann, C., Bidard, J.-N., Lazdunski, M. (1989a) Subtypes of K channels differentiated by the effect of K channel openers upon K channel blocker-induced seizures. Brain Res. 495: 189–192

Gandolfo, G., Gottesmann, C., Bidard, J.-N., Lazdunski, M. (1989b) K channel openers prevent epilepsy induced by the bee venom peptide MCD. Eur. J. Pharmacol. 159: 329–330

Gauldie, J., Hanson, J. M., Rumajanek, F. D., Shipolini, R. A., Vernon, C. A. (1976) The peptide components of bee venom. Eur. J. Biochem. 61: 369–376

Gauldie, J., Hanson, J. M., Shipolini, R. A., Vernon, C. A. (1978) The structure of some peptides from bee venom. Ibid. 83: 405–410

Gimenez-Gallego, G., Navia, M. A., Reuben, J. P., Katz, G. M., Kaczorowski, G. J., Garcia, M. L. (1988) Purification, sequence, and model structure of charybdotoxin, a potent selective inhibitor

of calcium-activated potassium channels. Proc. Natl. Acad. Sci. USA 85: 3329–3333

Gushchin, L. S., Miroshnikov, A. I., Martynov, V. I., Sviridov, V. V. (1981) Histamine releasing and anti-inflammatory activities of MCD-peptide and its modified forms. Agents Actions 11: 69–71

Hadjipetrou-Kourounakis, L., Yiangou, M. (1988) Bee venom, adjuvant induced disease and interleukin production. J. Rheumatology 15: 1126–1128

Hanson, J., Morley, J., Soria-Herrera, C. (1974) Anti-inflammatory property of 401 (MCD-peptide), a peptide from the venom of the bee Apis mellifera. Br. J. Pharmacol. 50: 383–392

Hider, R. C., Ragnarsson, U. (1981) A comparative structural study of apamin and related bee venom peptides. Biochim. Biophys. Acta 667: 197–208

Hider, R. C. (1988) Honeybee venom: A rich source of pharmacologically active peptides. Endeavour 12: 60–65

Jan, L. Y., Jan, N. J. (1989) Voltage-sensitive ion channels. Cell 56: 13–25

Jasani, B., Kreil, G., Mackler, B. F., Stanworth, D. R. (1979) Further studies on the structural requirements for polypeptide-mediated histamine release from rat mast cells. Biochem. J. 181: 623–632

Kumar, N. V., Wemmer, D. E., Kallenbach, N.R. (1988) Structure of P401 (mast cell degranulating peptide) in solution. Biophysical Chem. 31: 113–119

Lewis, R. S., Cahalan, M. D. (1988) The plasticity of ion channels: parallels between the nervous and immune systems. Trends in Neuroscience 11: 214–218

Lorenzetti, O. J., Fortenberry, B. (1972) Influence of bee venom in the adjuvant-induced arthritic rat model. Res. Commun. Chem. Path. Pharm. 4: 339–352

Moczydlowski, E., Lucchesi, K., Ravindran, A. (1988) An emerging pharmacology of peptide toxins targeted against potassium channels. J. Membrane Biol. 105: 95–111

Nakajima, T., Yasuhara, T., Uzu, S., Wakamatsu, K., Miyazawa, T., Fukuda, K., Tsukamoto, Y. (1985) Wasp venom peptides, wasp kinins, new cytotrophic peptide families and their physicochemical properties. Peptides 6 (Suppl.3): 425–430

Rehm, H., Lazdunski, M. (1988) Purification and subunit structure of a putative K channel protein identified by its binding properties for dendrotoxin I. Proc. Natl. Acad. Sci. USA 85: 4919–4923

Romey, G., Lazdunski, M. (1984) The coexistence in rat muscle cells of two distinct classes of Ca-dependent K channels with different pharmacological properties and different physiological functions. Biochem. Biophys. Res. Commun. 118: 669–674

Schmidt, R. R., Betz, H. (1989) Cross-linking of b-bungarotoxin to chick brain membranes. Identification of subunits of a putative voltage-gated K channel. Biochemistry 28: 8346–8350

Schweitz, H., Stansfeld, C. E., Bidard, J.-N., Fagni, L., Maes, P., Lazdunski, M. (1989) Charybdotoxin blocks dendrotoxin-sensitive voltage activated K channels. FEBS Lett. 250: 519–522

Somerfield, S. D. (1984) The concept of anti-inflammatory peptides. New Zealand Med. J. 97: 298–300

Stansfeld, C. E., Marsh, S. J., Parcej, D. N., Dolly, J. O., Brown, D. A. (1987) Mast cell degranulating peptide and dendrotoxin selectively inhibit a fast-activating potassium current and bind to common neuronal proteins. Neuroscience 23: 893–902

Taylor, J. W., Bidard, J.-N., Lazdunski, M. (1984) The characterization of high-affinity binding sites in rat brain for the mast cell-degranulating peptide from bee venom using the purified monoiodinated peptide. J. Biol. Chem. 259: 13957–13967

Ziai, M. R., Imberti, L., Kobayashi, M., Perrusia, B., Trinchieri, G., Ferrone, S. (1986) Distinct functional domains on the recombinant human immune interferon molecule. Cancer Res. 46: 6187–6190

Zurier, R. B., Mitnick, H., Bloomgarden, D., Weissmann, G. (1973) Effect of bee venom on experimental arthritis. Ann. Rheum. Dis. 32: 466–470