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Review Article

Anti-cancer and Anti-microbial and Neurological Effects Using Wasp Venom Peptides Agent: Review

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Abstract

Using of drugs have insufficient therapeutic effects on many diseases including cancer. The side effects derived from anti-tumor compounds are a result of their low specificity. Cancer is the major public burden all over the world. Anticancer drug developments from natural biological resources are ventured throughout the world. Many active principles produced by animals, plants and microorganisms have been employed in the development of new drugs to treat diseases such as great potential as anti-tumor agents. Wasp venoms are complex mixtures of pharmacologically and biochemically active components such as biogenic amines, peptides and proteins have been studied. Many researchers designed a new therapy based peptide binding of several amino acids from wasp venom for its potential use against breast cancer. This peptide has the ability to form pores in the cell plasma membrane, penetrate into the cell and finally, cause its death. Many bioactive substances were identified from wasp venom. These peptides showed anticancer, antimicrobial activities against bacteria and fungi. The present work reports the structural and functional characterization of the bioactive proteins and peptides in wasp venoms for cancer and microbial therapy.

Keywords: Cancer Therapy; Microbile; Wasp Venom; Mastoparan; Peptides

Introduction

A total of 1,638,910 new cancer cases and 577,190 deaths from cancer are projected to occur in last years [1]. In all types of cancer, genetic alterations give rise to changes in expression, activation or localization of regulatory proteins in the cells, affecting the signaling pathways that alter their response to regulatory stimuli and allow the unrestricted cell growth. Various therapies have been used for treating cancer such as chemotherapy, radiotherapy, immunotherapy and gene therapy [2] but still there is an urgent need of finding a better natural safe way to treat cancer with little effect on normal cells. Many active principles produced by animals, plants and microorganisms have been employed in the development of new drugs to treat diseases such as cancer. Among the animals that produce pharmacologically active molecules capable of interfering in human cellular physiology, the highlights are venomous arthropods, such as scorpions, bees, wasps, spiders, ants and caterpillars. The substances found in the venom of these animal's present great potential as anti-tumor agents.

New trends of natural therapy depend on Wasp venom compounds might become important sources to produce a novel medicine with fewer adverse effects as used against helminth parasite [3]. The antimicrobial peptide Polybia-MP1 (IDWKKLLDAAK QIL-NH2), or simply MP1 of animal venom has unexpectedly been shown to exhibit selective inhibition against several types of cancerous cells and, therefore, could prove advantageous in the development of novel therapy. Surprisingly, MP1 also selectively inhibits proliferating bladder and prostate cancer cells [4], and multidrug-resistant leukemic cells [5]. Recently, it has been observed that this peptide is cytotoxic against leukemic T lymphocytes and very selective in recognizing these cells compared to healthy lymphocytes [6]. The active components of Wasp Venom found to exhibit interesting bioactivities, such as antimicrobial, anti-inflammatory and antioxidant activities as well as anti-tumors. Also Wasp possess highly toxic venoms, which are a complex mixture of amines, small peptides and high molecular weight proteins, such as mastoparans, transportan, enzymes, allergens and toxins [3,4,7,8]. In this respect, the present review for understanding of the mechanisms, mode of action and future prospects regarding the use of new drugs derived from wasp venom for treatment cancer, microbial and pathogenic diseases.

Wasp venom

Wasps are arthropods bear a complex gland responsible for the production and injection of venom, which exhibits physiological, pharmacological and biochemical activities, playing a role in a variety of survival mechanisms such as defense against predators and prey capture, among others [8,11]. Even though wasp sting

may cause serious health problems, many studies have focused on the bioactive compounds present in wasp venom, such as biogenic amines, peptides and proteins [12]. Recently, different studies have reported the anti-cancer potential of these bioactive compounds. Among them, one of the most studied molecule is mastoparan, a 14-amino acid amphipathic peptide obtained from wasp venom and it has been reported to induce a potent mitochondrial permeability transition in the concentration range between 5 and 100 mM, by forming a permeability transition pore. The encapsulated mastoparan was able to release cytochrome c in the cell line studied, indicating its potential as an anti- cancer agent.

Wasp Venom Peptides

Mastoparan

Mastoparan is a class of multifunctional peptides found in solitary and social wasp venom, with its primary activity described in mast cell degranulation, giving the peptide its name [16]. Thus, these peptides exhibit a number of remarkable pharmacological activities, such as antimicrobial, antitumor, insulin-tropic and neurological effects [17-19].

The first Mastoparan was identified and chemically characterized by [16], when this molecule was isolated from the social wasp *Vespula lewisii*. Mastoparans are short cationic peptides with 10 to 14 amino acid residues, two to four lysine residues and C-terminal amidation, characteristics that are essential for proper peptide action [20,21]. These peptides can interact and penetrate biological membranes via the positively charged side-chains of their amphipathic α-helical structures [21]. In light of this property, Mastoparans were recently classified as cell-penetrating peptides (CPP) [22].

Crossing the BBB is a significant challenge in neuropharmacology. The BBB is responsible for regulating rain homeostasis through selective permeability that protects the CNS. However, these characteristics also affect drug delivery and bioavailability to the CNS. Advances in the fields of pharmacokinetics, molecular biology, nanotechnology and toxicology have resulted in strategies to facilitate the crossing of drugs through the BBB, thus, increasing drug concentration in the brain [23]. Cell permeable peptides (CPP), particularly Mastoparans, serve as vehicles for the delivery of different molecules and particles into the brain and neurons and have been studied in combination with compounds that act on the CNS [24].

With the aim of enabling neuroactive compounds to permeate the BBB, researchers have created new chimeric peptides (Transportan), connecting Mastoparans and the neuropeptide Galanin in two different ways. The first compound, named Transportan, is formed by 12 residues of Galanin and a full length Mastoparan connected by a lysine, resulting in a chimera with 27 residues [24]. The second compound, called Transportan 10, consists of seven terminal residues of Galanin and a full Mastoparan connected by a lysine residue [25]. Galanin, discovered in 1983, is a neuropeptide that in humans contains 30 amino acid residues and 29 in other species, for revision see [27]. Its name originates from the fusion of Glycin and Alanin, the N-terminal and C-terminal amino acids, respectively. Widely distributed in the peripheral and central nervous systems, Galanin has been associated with the pathophysiology of neurodegenerative diseases such as AD and Epilepsy [27]. Several studies report that the overexpression of Galanin detected in AD can preserve cholinergic striatal neuron function, which in turn may slow AD symptoms [27].

The chimeric construction of Transportan and Transportan 10 peptides has been used as a drug delivery system for Galanin in the CNS and as treatment for neurodegenerative diseases, acting as a neuroprotective agent. Another important function of Mastoparans is that they act as an antidote to one of the most powerful neurotoxins in the world, Botulinum toxin A (BoTx-A). If inhaled, only one gram of crystallized BoTx-A dispersed in the air can kill a million people [28]. Intoxication is so rapid and severe that some countries developed biological weapons containing BoTx for use in World War II. Intoxicated patients are treated with serum therapy. However, this does not reverse the toxic effects already induced in the organism [29].

As such, in an effort to treat this intoxication, a group of researchers employed Mastoparan 7 in a chimeric construction denominated Drug Delivery Vehicle-Mas 7 (DDV-Mas 7). Consisting of a non-toxic heavy chain fragment of BoTx-A and Mastoparan 7, this chimeric peptide induced neurotransmitter release in a culture of mice spinal cord neurons, reversing the effect of the BoTx-A and allowing Ach liberation, followed by muscular contraction [20].

Mastoparans also modulate G-protein activity without receptor interaction, currently considered a preeminent tool for the study and understanding of this complex intracellular signaling system [30-33].

Several neurological disorders, including Mood Disorders, Epilepsy, AD, and PD are related to G protein-coupled receptors [3-36]. Thus, over the last decade, natural, modified or chimeric Mastoparans have been used as a potential treatment for a number of neurological conditions.

Wasp Kinin

Another class of peptide frequently encountered in wasp venom is Kinin, composed of Bradykinin [BK] and its analogues, largely responsible for the pain caused after a wasp sting and the paralyzing action used for prey capture [37-39]. Naturally present in different animals, BK was first described as consisting of nine amino acid residues, with its primary activity described in mammal plate-

lets [40]. This small peptide plays an important role in controlling blood pressure, renal and cardiac function, and inflammation [41]. It is important to note that Kinin was the first neurotoxin component isolated from wasp venom. In addition, Kinin acts on the insect CNS, where it irreversibly blocks the synaptic transmission of nicotinic acetylcholine receptors [39-42]. Furthermore, Kinin components, produced via the kallikrein-kinin system, have been found in abundance throughout both the rat and human CNS attracting interest in neuroprotective research [43]. Two major Kinin receptor families have been identified: B2 and B1 receptors. Their expression is low under normal conditions, but is up-regulated following injury, infection and inflammation [44]. Meanwhile, BK has also been shown to possess anti-inflammatory (neuroprotective) properties, suppressing the release of inflammatory cytokines (TNF-α and IL-1β) from microglia in *in vitro* assays [43]. According to these authors, BK modulated microglial function by negative feedback for cytokine production, increasing prostaglandin synthesis and causing greater microglial cAMP production [43]. BK can also be beneficial after ischemic stroke, particularly if administered in the latter stages as opposed to the initial phases, where its harmful effects include inflammatory response and neurogenic inflammation [45]. It is noteworthy that molecular and functional evidence has suggested that interaction with B1 receptors may provide a new therapeutic approach as anti-tumor and anti-microbial diseases by effect of immune cells lymphocytes T [45,62,63]. This indicates that the neuroprotective mechanism initiated by BK may also inhibit the mitochondria-mediated apoptotic pathway [63]. The neuroprotective role of BK has also been reinforced by evidence of its action in the retina, protecting against neuronal loss induced by glutamatergic toxicity. This BK-induced protection caused a downstream reaction in NO generation and an upstream reaction in radical oxygen generation [46]. As observed, BK agonists may provide a new platform for drugs designed to treat neurodegenerative disorders that involve microglial activation, such as PD and acute brain damage. In this respect, wasp venom contains a multitude of Kinins with different activity potency profiles. A good example is Thr6-Brady kinin, a compound isolated from several wasp venom samples. The single substitution of serine for threonine in this compound results in enhanced action when compared to BK. According to [47], this peptide displays remarkable anti-nociceptive effects when injected directly into the rat CNS; it is approximately three times more potent and remains active longer than BK [47]. These results can be explained by a more stable conformation in its secondary structure and/or the modification may protect against hydrolysis through neuronal kininases, preserving the effect of the peptide on B2 receptors [47,48].

Polyamine toxins

Polyamine toxins are a group of low molecular weight (<1 kDa), non-oligomeric compounds isolated primarily from the venom of wasps [49,50]. The first polyamine toxin described, Philanthotoxin-433 (PhTX-433), was isolated from the venom of the wasp *Philanthus triangulum* [51]. These small natural molecules exhibit a number of biological activities and have been used as tools in the study of ionotropic glutamate (iGLU; AMPA) and nicotinic acetylcholine (nACh) receptors since the 1980s [50,52,53]. Interest is centered on its action as a non-selective and potent antagonist of glutamate receptors in the invertebrate and vertebrate nervous system [52-54]. Moreover, it is believed that the abnormal activation of iGLU receptors is involved in neurological and psychiatric diseases such as AD, PD, Stroke, Depression, Epilepsy, Neuropathic Pain and Schizophrenia [55,56].

With respect to iGLU, current polyamine toxins (PhTXs) and their derivatives have the ability to differentiate which AMPA receptors are in fact permeable to Ca^{2+} ion, acting as a non-selective open-channel blocker [50,57]. As a result, PhTXs can control the excessive opening of over activated ion channels (due to pathological conditions) and block the exaggerated influx of calcium, culminating in neuroprotection [53,58]. Interestingly, this mechanism of action is similar to that of Memantine, a drug used in the symptomatic treatment of moderate to severe AD [59]. Thus, the existence of a drug that has obtained good clinical results and its similarity with polyamine toxins illustrates the potentially promising role of these molecules and highlights the need for further research. Recently, a computational model approach was devised to better understand how polyamine toxins interact with ion channels coupled with glutamate receptors [60]. This study found that these molecules could bind to the narrowest central region of the ion channel and block local ion flow. Membrane potential is important in toxin-receptor interaction, and as such, polyamine toxins are generally highly voltage-dependent blockers of iGLU [60]. In this regard, recently developed fluorescent templates using polyamine toxin analogues to visualize these ligands in iGLU of living tissue [61].

Discussion

Several families of bioactive peptides have been identified in wasp venoms. These peptides are bradykinin-like peptides, chemotactic peptides and mastoparans [6-9]. Local or systemic reactions may come from these biologically active peptides. These major actions include, limited in vitro antimicrobial effects [10] and inflammation induction by lysing cell membrane or stimulating mast cell degranulation, histamine release and consequent vasodilation, and increasing neutrophils and T helper cells chemotaxis [11-14]. All of these effects are related with cardiovascular system, nervous system and immunological system of mammals, including humans.

The purified and characterized a novel bioactive peptide, vispin containing 44 amino acid residues. It exerts contractile function on isolated ileum smooth muscle. Bradykinin-like peptides in wasp venoms have also function to induce contraction of ileum smooth muscle. They exert their bioactivity by interacting with bradykinin

receptors. All members of bradykinin-like peptides share conserved –PPGF(T/S)P(F/L)- structure at their C-terminus [15]. The wasp's venom effect may be due to mastoparan, which targets the mitochondrial membrane and causes mitochondrial permeability transition to mediate its tumor cell cytotoxicity. Several studies have demonstrated the antitumor activity of mastoparan and analogs in vitro [64] and one possible way to deliver mastoparan and avoid side effects was presented by Wu and Li [65]. Wasp venom contains numerous bioactive substances that are of importance to the animal for hunting and defending against intruders, but have also attracted attention because of their potential physiological, pharmacological, and therapeutic applications. Many wasp venom-derived peptides that are known, mastoparan and mastoparan-like peptides are the most active wasp venom components. The majority of mastoparans are 14 amino acids in length, most of which are the hydrophobic residues leucine, isoleucine, valine, and alanine.

Pharmacologically, mastoparans also represent a promising group of small peptides, with those mastoparans that have been characterized variously displaying broad-spectrum action against microorganisms, inhibitory effects against tumour proliferation, and stimulating serotonin release from platelets and mast cell degranulation [32]. Importantly, recent studies have also shown that mastoparans are effective against some clinically resistant microbial strains. For instance, Lin and colleagues demonstrated that multidrug-resistant *Acinetobacter baumanni,* one of major contributors to nosocomial infections, is compromised by mastoparan-AF in low dosages [66].

However, the promise shown by mastoparans as potential drug candidates is offset currently by their haemolytic activity and other reported toxic effects [16]. A useful strategy in this regard is targeted engineering, which proximately aims to optimize therapeutic activity, in part by reducing toxicity toward normal cells, and ultimately enables us to further explore the structure-function interrelationship of small peptides with the goal of improving targeted design changes. Alternatively, short foreign peptide sequences can also be added to antimicrobial peptides as part of a directed therapeutic drug design, particularly CPP/PTD application (frequently artificial sequence (polyarginine and polylysine)) to improve drug delivery, but also the virus fragments VP22 and Tat or the insect peptide penetratin [67,68].

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