Recent Patents in CNS Drug Discovery: The Management of Inflammation in the Central Nervous System

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Abstract: In recent years, one of the major advances in terms of our understanding of the pathology underlying many neurological conditions has been the realisation that inflammation may play a major role in many acute and chronic conditions. Inflammation is not only involved in acute CNS conditions, such as stroke and traumatic injury, but it is also a central factor in chronic and neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease and multiple sclerosis. There are some key differences between inflammatory processes within the CNS (neuroinflammation) and peripheral inflammation, partly due to the natural compartmentation of the brain by the blood-brain barrier. As a result of these differences, the classical anti-inflammatory agents (steroids and NSAIDs) have not played a major role in the management of CNS inflammatory conditions. In order to address this clinical need, there is significant interest in developing novel anti-inflammatory agents that may help prevent or ameliorate CNS inflammation. In this review, the authors focus on disclosures from the patent literature to give a broad overview of the different approaches that are being taken to try and develop more effective and selective anti-inflammatory agents to manage acute and chronic inflammation in the CNS. A variety of approaches are discussed including modulating the activity of various inflammatory mediators such as cytokines, chemokines and kinins, targeting toll-like receptors as a possible therapeutic intervention, and novel approaches to managing the actions of eicosanoids in neuroinflammation.

Keywords: Brain injury, neuroinflammation, cytokines, chemokines, bradykinin, tachykinins.

BACKGROUND

One of the key advances in our understanding of central nervous system (CNS) pathologies in recent years has been the realisation that inflammation may play a major role in many acute and chronic conditions. Inflammation is now considered critically important in some of the most significant and prevalent neurological disorders that present in the clinic today. Perhaps not surprisingly, inflammation is known to play a role in acute CNS conditions such as injury (e.g. traumatic, ischaemic) and infection (e.g. meningitis, HIV infection, etc) [1-3]. However, it is also recognised as a key factor in chronic and neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and more recently epilepsy [4-7]. Whilst inflammation is now recognised to play a major role in many CNS conditions, to date the standard anti-inflammatory agents, namely corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), have only played a limited role in the management of these conditions. There are exceptions to this. For example, corticosteroids may be effective in treating intractable paediatric epilepsy, and for controlling peritumoural oedema [8,9]. In addition, the recognized correlation between the long-term use of NSAIDs and a reduced incidence of Alzheimer's disease and Parkinson's disease provided evidence to support the inflammatory nature of these neurodegenerative conditions [10,11]. However, the full potential value of controlling inflammation within the CNS is not achieved with the currently available anti-inflammatory agents. Indeed, the results of one recent, large clinical trial using celecoxib and naproxen have shown no benefit in terms of preventing Alzheimer dementia [12].

There are factors that underlie the limited efficacy of classical anti-inflammatory agents to manage inflammation within the CNS. These may include a basic lack of efficacy in this system, a poor balance between systemic side effects and any potential beneficial effects, and a poor balance between pro- and anti-inflammatory effects within the CNS [13]. In all tissues there is a fine balance between the protective effects of inflammation and the potential detrimental effects. However, within the CNS this balance is even more critical, and it appears that special mechanisms have evolved in order to protect neuronal connections in the face of an inflammatory response [14-16]. For example, a delicate balance between neuroprotective and neurodegenerative actions may underlie the negative outcomes observed in some of the clinical trials for NSAIDs in neurodegenerative disorders. In peripheral tissues, the inducible form of cyclooxygenase, cyclooxygenase-2 (COX-2), is considered to be the preferred target for NSAIDs. Selective COX-2 inhibitors may help to avoid many of the side effects of non-selective NSAIDs, such as gastric ulceration, that may be associated with inhibition of cyclooxygenase-1 (COX-1). However, there is evidence that in the CNS COX-2 may exert a neuroprotective role, whilst it is COX-1 that has the pro-inflammatory or neurodegenerative effect [13, 17]. If this is the situation, then this would explain why COX-2 selective agents lack efficacy, whilst non-selective NSAIDs may demonstrate efficacy [10]. Furthermore, it would suggest that for controlling neuro-

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degenerative disorders, selective COX-1 inhibitors would be the most effective agents [17]. Therefore, in order to manage the inflammation associated with CNS disorders, there is a need for an improved understanding of the inflammatory mechanisms and mediators associated with the central nervous system. In recent years a number of novel pharmacological agents have been developed that specifically target some of the inflammatory processes associated with the CNS. As a result, there is the potential for some of these agents to address the significant unmet medical need posed by many severe neurological conditions.

Classically, the central nervous system is viewed as being shielded from the immune system by the blood brain barrier (BBB), conferring upon it an "immuno-privileged" position within the body. The CNS does certainly "enjoy" a different immune status from other organ systems within the human body, a situation that has presumably evolved as a protective mechanism. Given the brain's low capacity for regeneration, it may serve as a mechanism to protect the brain's delicate neuronal connections from collateral damage during an inflammatory response [18,19], or as a means of reducing the risk of autoimmune attack [15]. However, this immuno-privilege is now recognised as being more of a relative rather than an absolute status [19]. Firstly, the central nervous system has its own, dedicated immune system whose function is mediated via glial cells [14, 20]. Secondly, the BBB is not an absolute barrier, and altered BBB function may be one of the factors that leads to a loss of the brain's immune-privileged status [19].

Glial cells, including astrocytes and microglia, play an important and supportive physiological role within the CNS [20]. Astrocytes contribute to normal neuronal function by supplying precursors for the synthesis of amino acid neurotransmitters, the uptake of amino acid transmitters following release, and the buffering of ionic changes, particularly K^+ ions, in the extracellular fluid. Astrocytes are also thought to be a major contributor to the defence against oxidative damage in the brain. Microglia are phagocytic cells, serving as the macrophages of the CNS. They engulf and remove invading microorganisms, as well as injured or dead neurons. These glial cells may also engage in inflammatory processes that serve to defend the CNS from pathogens, as well as aid in its recovery from insult and injury [21-24]. The glial cells represent the first line of defence for the CNS, providing an innate immune response and the potential to activate an adaptive immune response [22-24]. However, whilst the inflammatory response mediated via the glial cells, commonly referred to as neuroinflammation, may help the CNS recover from stress and injury, an excessive activation of these mechanisms can result in a vicious cycle of severe, chronic neuroinflammation that may have deleterious effects within the CNS, which may promote or propagate neurodegeneration [21, 24, 25]. There is a growing body of evidence to suggest that excessive or inappropriate neuroinflammation plays an active role in chronic neurodegenerative disorders such as Alzheimer's and Parkinson's disease [26]. Activated microglia secrete a variety of soluble factors. Some of these, such as glia-derived neurotrophic factor, may have beneficial, neuroprotective actions. However, there are a significant number of factors released by activated glial cells that have pro-inflammatory and neurotoxic actions, and they may play a key role neurodegeneration [26-28]. As a result, there is a significant interest in the mediators which regulate neuroinflammation, since they represent a promising drug development target for novel therapies aimed at preventing or controlling neurodegenerative disorders [25, 27, 28].

Glial-cell mediated inflammation represents one mechanism by which inflammation may occur within the CNS, and is probably responsible for chronic inflammatory conditions. Another mechanism by which inflammation may occur in the CNS is compromised or altered BBB function. As mentioned earlier, the BBB is not an absolute barrier, but it does play a key role in compartmentalising and controlling immune responses [29]. Whilst the BBB does limit and control leukocyte infiltration, and as such CNS inflammation, some cellular infiltration may occur, and not just in situations where there is BBB dysfunction [30]. In terms of functional arrangement, solute movement is controlled at the level of the capillaries, and here specialised tight junctions between the endothelial cells, as well as a close association between the endothelial cells and astrocytic foot processes, are a key aspect of normal BBB function [31]. In contrast, the primary site of leukocyte recruitment into the CNS is at the level of the post-capillary venules [29]. Here the tight junctions are less specialised, but there is evidence that leukocytic movement may occur via a trans-cellular route [32]. At the level of the post-capillary venule there is a compartment, or perivascular space, formed by the glia limitans, which separates the vessel wall from the neuropil. The glia limitans provides a strong functional barrier between the perivascular space and the neuropil, and while it may be relatively easy for leukocytes to enter the perivascular space, they may accumulate there without passing on into the neuropil. Indeed, this pattern is clearly seen in multiple sclerosis [33]. The factors that enable cellular penetration of the glia limitans and subsequent intraparenchymal inflammation are of significant interest. These may include the induction of perivascular apoptosis associated with activation of the CD95 receptor [34], or the expression of specific matrix metalloproteinases [35].

Although they are not numerous, perivascular cells, or perivascular macrophages, may represent important immunoregulatory cells that help to link the peripheral immune system with the CNS. These cells may respond to disturbances within both the CNS and the peripheral immune system, and are activated in a variety of situations including CNS inflammation and injury. Various immunologic roles have been ascribed to the perivascular cells, including that of antigen-presenting cells [36], and there is an interest in the role they play in CNS disorders, particularly where BBB function is compromised. These cells are also a critical CNS target in HIV infection [37].

Given the significant role the BBB plays in regulating normal immune function and inflammatory responses, there is a significant interest in factors that may alter normal BBB function, and hence affect the brain's normal immune status [19, 38, 39]. Following acute insults to the brain, such as traumatic or ischaemic events, BBB function may become compromised for a period of time, allowing for the entry of immune cells from the circulation [25]. The controlled or

uncontrolled reperfusion of the brain following an ischaemic event probably represents a major factor in compromising BBB function, leading to reperfusion injury [40]. Transmigration of leukocytes following blood brain barrier disruption may result in the activation of glial cells in the CNS. Both the infiltrating peripheral immune cells and activated glial cells engage in the production of cytokines, potentially promoting neuroinflammation [41]. In addition, this transient alteration in BBB function contributes to the vasogenic component of cerebral oedema [42]. Compromised BBB function is considered to facilitate the acute inflammatory response associated with conditions such as traumatic brain injury, stroke and epilepsy. As a result, the BBB may also serve as a target for anti-inflammatory drug development, since agents that are capable of restoring or maintaining its integrity could help ameliorate the acute phase of CNS inflammation [43]. Altered BBB function may not only underlie actue CNS inflammation, but may also be a factor in chronic CNS conditions including Alzheimer's disease, Parkinson's disease and cerebral metastases [31, 38].

The aim of the current review is to give a broad outline of some of the different approaches that are currently being developed in order to ameliorate or prevent the deleterious effects of inflammation within the central nervous system. In it, we have tried to identify some of the key molecular or cellular targets that yield effect anti-inflammatory agents.

NOVEL APPROACHES TO CONTROLLING NEUROINFLAMMATION

There are many reports in the scientific literature to suggest the potential benefit of anti-inflammatory agents, particularly in conditions such as Alzheimer's and Parkinson's disease [44, 45]. With the realization that inflammation may play a central role in many neurological conditions, there has also been much speculation in the patent literature regarding the potential benefits of a whole range of anti-inflammatory agents in helping to manage these conditions. Recently, Monje and Palmer [46] provided evidence to support some of the deleterious effects of neuro-inflammation, particularly in relation to the process of neurogenesis. Their patent application provides evidence that anti-inflammatory agents, such as NSAIDs, may ameliorate neuroinflammation, and indirectly facilitate neurogenesis. These studies add weight to the growing body of evidence that drugs targeting neuroinflammation may have an important role to play in the treatment of neurological disorders. However, whilst there are benefits to be derived from anti-inflammatory agents, the appropriate molecular targets must be carefully identified [10,13,17].

MODULATORS OF CYTOKINE ACTIVITY

Cytokines, such as Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), Tumor Necrosis Factor alpha (TNF-α) and Transforming Growth Factor beta (TGF-β) have been clearly identified as being involved in neuroinflammatory processes, with IL-1β and TNF-α in particular appearing to have a very central pro-inflammatory effect [47,48]. As a result, there is significant interest in agents that are capable of modulating the activity of these inflammatory mediators [49]. A significant volume of research has focused upon antagonists and antibodies directed against IL-1β and TNF-α in particular, and a large range of small molecules and antibodies capable of inhibiting the actions of IL-1β have been described in the patent literature [50, 51]. Similarly, there has been much focus on developing agents that block the actions of TNF-α [52, 53], and the potential use of such agents to ameliorate inflammation within the CNS has been claimed [53] .

At present there are a few anti-cytokine therapies available in the clinic. These biopharmaceutical agents include infliximab and adalimumab, which are monoclonal antibodies directed against TNF-α, etanercept, which is a TNF receptor linked to IgG, and anakinra, which is an IL-1 antagonist. These agents have been viewed as a breakthrough in the treatment of peripheral chronic inflammatory disorders, and are primarily aimed at managing rheumatoid arthritis [54]. To date, the use of these agents has been quite limited, mainly due to their cost. One of the concerns relating to the use of these agents was that they may have a significant immunosuppressant action, thereby predisposing patients to infection and latent disease. It now appears that this concern has some foundation, with the FDA issuing an alert (Sept 2008) to healthcare professionals that histoplasmosis and other invasive fungal infections are not consistently recognized in patients taking TNF-α blockers resulting in delays in administering appropriate remedial treatment. There have been some reports of blood dyscrasias, and interestingly, demyelinating disorders within the CNS.

Recently Palladino and colleagues [55] have described how a family of compounds derived from acanthoic acid act as potential modulators of IL-1β and TNF-α. Acanthoic acid is a pimaradiene diterpene isolated from the Korean medicinal plant, Acanthopanax koreanum. Extracts of Acanthopanax have been used in traditional Korean medicine to treat rheumatic disease. Acanthoic acid has been shown to have anti-inflammatory actions through reducing IL-1β and TNF-α production [56]. Palladino *et al.* [55] provide data to support the potential anti-inflammatory actions of acanthoic acid through modulation of cytokine activity.

Another potential therapeutic target for preventing the pro-inflammatory actions of IL-1β is inhibition of IL-1β converting enzyme (caspase-1), resulting in reduced production of IL-1β and IL-18 [57]. The selective ICE inhibitor, Prainacasan, has been shown to inhibit the pro-convulsant effects of IL-1β in a rodent model of brain seizures [58]. Wannamaker and colleagues [59] have disclosed a novel class of componds that are selective inhibitors of caspase, particularly ICE. The potential use of these agents for inhibiting interleukin-1- mediated pathologies, including inflammatory diseases, autoimmune diseases and degenerative diseases, is disclosed [59].

Another approach to regulating the actions of TNF-α has been disclosed by Levite and colleagues [60]. It has been reported that K+ ions may play an important role in regulating cytokine production by activated macrophages [61]. Levite and colleagues [60] disclose that modulation of the KV1.1 voltage-gated potassium ion channel in T-cells can in turn modulate the synthesis and secretion of TNF-α. Inhibition of this K^+ ion channel results in a significant

production of TNF-α, and this may be of value in terms of enhancing an inflammatory reaction directed against cancerous cells or infectious organisms. Conversely, opening this ion channel can prevent the excessive release of TNF-α, and hence such agents may be useful in inflammatory conditions where excessive production of TNF-α is playing a key role. Another novel approach to regulating TNF-α activity has been disclosed by Kettling and colleagues [62]. The objective of their invention was to provide protease enzyme that selectively targets human TNF-α, inactivating the cytokine in a specific manner. This TNF-α-targeting protease, which can be preferentially expressed in a microbial expression system, provides another route for decreasing the potentially harmful, pro-inflammatory effects of TNF-α.

High mobility group box 1 (HMGB1) is a nuclear DNA-binding protein which is postulated to be a pro-inflammatory cytokine within the CNS, primarily due to its ability to stimulate the release of other pro-inflammatory cytokines, including interleukin-1beta (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNFα) [63,64]. Tsung and colleagues [65] have described how pretreatment with HMGB1 protein, and analogues of this protein, may protect against reperfusion injury following a period of ischaemia. The patent application indicates that in mice, pretreatment with HMGB1 prior to a one-hour period of ischaemia and subsequent six-hour reperfusion period, results in a significant reduction in the serum levels of the pro-inflammatory mediators TNFα and IL-6. Serum levels of Il-6 are considered to be a valuable marker of CNS inflammation and patient prognosis. The invention provides for the use of HMGB1 to protect organs, including the brain, from injury caused by ischaemia, reperfusion and trauma.

An understanding of the factors that influence T helper cell responses has been an important focus in immunology [66,67]. The central role of interleukin-12 (IL-12) in the generation of T helper cells has long been appreciated, but subsequent studies have indicated that two cytokines closely related to IL-12, IL-23 and IL-27, also regulate T-cell responses [68]. Importantly, IL-27 has a role in limiting the intensity and duration of adaptive immune responses [69]. Many studies have focused on the factors that influence the development of the IL-17-producing T helper cells associated with autoimmunity, such as experimental autoimmune encephalitis, but little is known about the cytokines that antagonize these responses. Chronically infected IL-27 receptor-deficient mice may develop a severe neuroinflammation that is associated with a prominent IL-17 response. Hence IL-27, a potent inhibitor of T helper cell development, may be a useful target for treating inflammatory diseases mediated by these cells. As such, there is an interest in IL-27 and its receptor, WSX-1, in terms of a potential mechanism for inhibiting inflammation [70]. Hunter and Stumhofer [71] have disclosed that WSX-I, the cytokine receptor that binds IL-27, may have clinical implications for T cell-mediated inflammatory disorders, and represent a novel target for immune based therapies. They have outlined a number of approaches that could be used to mimic or enhance the inhibitory actions of IL-27. These include the fusion protein, WSX-IFc, which is able to enhance the ability of IL-27 to inhibit T cell production of IL-2 and IFNγ. Recombinant p28 (or IL-30), while it is not as efficient as IL-27, is also able to antagonize the production of IL-2 and IL-17. They propose that p28 alone, modified, or as part of another molecule or complex that includes WSX-I, could represents a useful therapeutic approach to modulate cells of the immune system.

CHEMOKINES

Chemokines are pro-inflammatory proteins. They act primarily as chemoattractants and activators of specific leukocyte cell subtypes [72]. Whilst individual chemokines only target certain leukocytes, as a family they target the entire spectrum of leukocytes. Chemokines produce their effects via G-protein coupled chemokine receptors, and there is increasing evidence suggesting that these chemokine receptors are also involved in neuronal death [73]. Chemokine-induced neuronal death may occur either indirectly, through the activation of microglia, or directly via the activation of neuronal chemokine receptors. In the brain, chemokine receptors are found associated with microglia as well as astrocytes, oligodendrocytes and neurons. Chemokines have been implicated in a wide variety of neurological conditions. They are secreted in animal models of acute injury (traumatic injury, ischaemic injury), as well as chronic conditions, such as multiple sclerosis and Alzheimer's disease. Two significant members of the chemokine family appear to be MCP-1 (monocyte chemoattractant protein-1; CCL2) and RANTES (regulated on activation, normal T expressed and secreted; CCL5). Inhibition of these inflammatory mediators may be of value in a number of clinical scenarios including inflammatory conditions within the CNS [74]. Bower and colleagues [75] have described the synthesis of small molecule antagonists of the CCR2b receptor for which MCP-I is one of the known ligands. The applicants have disclosed that piperidine-piperazine compounds contain a cyclic moiety that is of value in antagonizing C-C chemokine receptors in general, and the CCR2b receptor in particular. Such agents may have significant potential as anti-inflammatory agents given the role that chemokines play in immune and inflammatory responses

Another approach to limit chemokine-mediated inflammatory disorders has been described by McDonald and colleagues [76]. Their invention covers the synthesis of a conjugate made up of a chemokine receptor ligand and a selective toxin, which they propose may be used to treat diseases associated with the activation, proliferation and migration of immune effector cells, including those cells that produce secondary tissue damage. It is proposed that the therapeutic agent would be directly toxic to the cells that promote secondary tissue damage, such as mononuclear phagocytes, dendritic cells, leukocytes and lymphocytes, thereby suppressing the proliferation, migration and activity of these cells. The toxin would be conjugated with a ligand for a specific chemokine receptor thereby enabling the selective targeting of the toxic agent. The inventors claim that the conjugates described within the patent would bind to the relatively small cell populations that are specifically associated with inflammatory disorders or inflammatory processes.

TOLL-LIKE RECEPTORS

Toll-like receptors (TLRs) are a key element in our innate immune response within the CNS [22, 23]. They are directly involved in detecting pathogen invasion or tissue damage, and in initiating a response to the challenge. TLRs recognize distinct microbial components (pathogen-associated molecular patterns; PAMPs), and activate intracellular signaling pathways that induce the expression of host inflammatory genes [77]. Toll-like receptors, unlike antigen receptors, are encoded in our DNA, and are expressed on the surface of antigen-presenting cells, dendritic cells and macrophages. Activation of these receptors triggers the production of the main pro-inflammatory cytokines, TNF-α and IL-1β, as well as the release of other mediators such as histamine and prostaglandins [78].

There is now considerable interest in developing novel pharmaceutical agents that target the TLRs in order to try and control inflammatory disease. Initially, extracellular TLR agonists were designed to compete with the natural microbial ligands for these receptors. More recently, research has begun to focus on modulating intracellular signaling pathways of the TLRs [79]. TLRs are able to stimulate the release of either immuno-stimulatory or immuno-modulatory molecules. The immuno-stimulatory properties of TLRs are being examined for their ability to generate tumour-specific immune responses directed against cerebral tumours, whilst the immuno-modulatory properties are being investigated for their ability to suppress the acute inflammatory responses associated with ischaemic insults. A third component of TLR signaling has also begun to emerge, and this pathway exerts a direct neuroprotective effect. As a result, there is a growing interest in TLRs since they may represent novel targets for the treatment of neurological disease [80].

Recently Van Noort and colleagues [81] have disclosed the use of TLR3 agonists for the treatment of neuro-degenerative disorders. There is evidence that TLR3-mediated responses can be distinct from the responses mediated by other TLR family members by being linked to a different signaling pathway. In response to most PAMPs, TLRs typically activate the NF-κB-mediated pathway leading to the production of TNF-α, IL- lβ, IL-6 and nitric oxide. This typical antimicrobial host defence response is designed to start the pro-inflammatory innate immune responses and eventually the antimicrobial adaptive immune responses. However, it has been shown that TLR3 signaling in human mast cells not only fails to trigger TNF-α or IL- lβ, but instead inhibits degranulation of these cells as well as their attachment to the extracellular matrix. The present inventors [81] have shown that activation of TLR3 on human astrocytes and fibroblasts results in a repair response which consists of enhanced production of a variety of anti-inflammatory, anti-fibrotic, pro-angiogenic, chemotactic and neuroprotective mediators that, together, support regenerative responses. In addition, they have shown that stathmin and stathmin-like proteins can act as activator or agonist for TLR3 or can activate TLR3-mediated signaling. The stathmin-activated TLR3-mediated response of astrocytes includes production of a range of neuroprotective, antiinflammatory, angiogenic and chemotactic mediators that support and promote regeneration.

KININ ANTAGONISTS

Kinins are a group of peptide mediators that, amongst other effects, have a pro-inflammatory action [82]. Some of their inflammatory effects are mediated via the vasculature where they promote inflammation by causing vasodilation and increased vascular permeability. There are two distinct families of kinins, the bradykinins and the tachykinins. The bradykinins are formed by cleavage of the plasma globulin, kininogen, by plasma and tissue proteases known as kallikreins. The active peptides formed by this proteolytic cleavage are bradykinin and kallidin (lysyl bradykinin). These kinins produce their effects through bradykinin receptors, with two subtypes of the receptor having been identified, B_1 and B_2. B_1 receptors are normally only expressed in very low levels, but are induced in inflammed and damaged tissues by cytokines such as IL-1β. There has been significant interest in developing non-peptide antagonists of the bradykinin receptor, given the potential ability for such agents to have anti-inflammatory and analgesic actions [83]. The potential role for these agents to manage neurological disorders that exhibit an inflammatory component has also been mooted [84], although there is also some evidence to suggest that bradykinin may have anti-inflammatory and neuroprotective effects in the central nervous system by modulating microglial function [85]. A number of groups have been successful in developing peptide [86] and non-peptide antagonists of the bradykinin receptor [87,88], and these patents all raise the potential use of such agents for managing neuroinflammation, particularly that associated with traumatic brain injury.

The tachykinins, which include substance P and neurokinin A, are released from nerves in the active form, and produce their effects via tachykinin receptors. Substance P is an abundant neurotransmitter, being associated with both the peripheral and central nervous systems. In the periphery, it is the predominant neurotransmitter found in nociceptive nerves. The release of substance P, and other neuropeptides, from sensory nerves is thought to play a significant role in the neural component of inflammation, neurogenic inflammation [89]. Indeed, it was found that mice which lack the receptor for substance P (tachykinin NK1 receptor) fail to exhibit normal inflammatory responses. As with bradykinin, there is significant interest in developing non-peptide antagonists of substance P, because of the potential of such agents to have analgesic and anti-inflammatory actions [90]. The first successful synthesis of a non-peptide antagonist was by Pfizer [91], but many other agents have been developed subsequently and are described in the patent literature [92-94].

There has been growing evidence in the scientific literature that substance P may play a significant role in the central nervous system, both from a physiological and a pathological angle. Its role in emesis has been clearly established clinically, with NK1 antagonists having very potent anti-emetic actions. There is also good evidence that NK1 antagonists have anti-depressant effects [90]. From the aspect of inflammatory conditions, there is growing pre-clinical evidence that substance P may be an important mediator of neuroinflammation in the CNS. NK1-receptor antagonists are capable of exerting vascular-mediated anti-

inflammatory effects through reducing the expression of the adhesion molecules ICAM-1 and VCAM-1 on vascular endothelium [95]. Adhesion molecules may play a critical role in leukocytic movement through the BBB. Nessler and colleagues [96] have shown that NK1 antagonists can suppress autoimmune encephalomyelitis. There is also evidence that NK1 antagonists can ameliorate the inflammation associated with acute injury to the brain, particularly through maintaining the integrity of the BBB [97,98]. Given the putative role of substance P in CNS pathologies described in the research literature, most patents describing the synthesis of these antagonists have cited their potential value in treating CNS disorders [92-94, 99, 100]. In terms of the patent literature, the best evidence for the value of NK1 antagonists in managing acute inflammation in the CNS comes from *in vivo* studies of traumatic brain injury, where it is demonstrated that NK1 antagonists are able to reduce cerebral oedema through maintaining integrity of the BBB and, as a result, significantly improve functional outcome [101, 102].

EICOSANOIDS

The eicosanoids are a family of mediators generated from phospholipid precursors. In addition to their physiological roles, they represent important mediators and modulators of inflammation, and have constituted one of the major targets for anti-inflammatory therapies [103]. The principle eicosanoids are the prostaglandins, the thromboxanes and the leukotrienes. Historically, the main target for anti-inflammatory agents directed against these mediators has been the enzyme, cyclo-oxygenase, which is involved in the production of prostaglandins and thromboxanes. More recently leukotrienes and the lipoxygenase pathway have become targets for anti-inflammatory agents, such as montelukast [104,105]. These agents may have some value in chronic inflammatory conditions, such as asthma, where the leukotrienes are potent spasmogens. Another group of mediators produced by the lipoxygenase enzyme are the lipoxins. They are of interest because of their anti-inflammatory actions and their ability to resolve inflammation, presumably by their ability to oppose the action of leukotriene B4 [106]. Serhan and colleagues [107] have disclosed the anti-inflammatory action of these agents, and the approaches to the isolation and purification of compounds, such as neuroprotectin D1. Interestingly, aspirin can stimulate the synthesis of lipoxins, which may contribute to some of its anti-inflammatory effects [108].

Clasically, non-steroidal anti-inflammatory drugs have played little role in the management of CNS inflammatory disorders. However, there is growing clinical evidence to suggest that they may have a beneficial effect. There is a well recognized correlation between the long-term use of NSAIDs and a reduced incidence of both Alzheimer's and Parkinson's disease [11, 109]. This evidence has helped support the idea, not only that inflammation is an important component of Alzheimer's disease, but that neuroinflammation in general is an important target for drug discovery [110].

During brain inflammation prostaglandins are produced by activated microglia [13]. However, as with some other inflammatory mediators, they are capable of both pro- and anti-inflammatory effects. Prostaglandins may have a neuroprotective effect through the elevation of neuronal cAMP levels. In addition, they can decrease the production of pro-inflammatory cytokines, and increase the secretion of anti-inflammatory cytokines. However, there is also a body of evidence suggesting that NSAIDs may have a protectant effect against neurodegeneration. This is still a very controversial area, with contradictory evidence arising from the clinical trials that are being conducted [10,12,111]. Nonetheless, there are possible explanations for this apparently contradictory evidence. One hypothesis is that there may be an over-expression of the inducible form of cyclo-oxygenase, COX-2, in both acute inflammatory conditions, such as hypoxia and ischemia , as well as chronic diseases, such as Alzheimer's disease, and this contributes to the neurotoxicity [112]. As a result there was a particular interest in the potential role of COX-2 inhibitors in preventing neurodegeneration [113]. However, the results of clinical trials with the COX-2 selective agents have been disappointing [12, 111]. As discussed earlier, there is evidence that in the CNS COX-2 may exert a neuroprotective role, whilst it is COX-1 that has the pro-inflammatory, or neurodegenerative effect [13, 17]. If this is the situation, this could explain why COX-2 selective agents lack efficacy, whilst non-selective NSAIDs may demonstrate efficacy [10]. Furthermore, it would suggest that for controlling neurodegenerative disorders, selective COX-1 inhibitors would be the most effective agents [17].

The lipoxygenase pathway and leukotrienes may also play a role in neurological disorders [114]. Nozaki [115] has disclosed that leukotriene antagonists, particularly antagonists of the leukotriene C4 and D4 receptors, may have a role to play in managing brain inflammation. He has disclosed the results of *in vivo* studies which show that these agents may prevent the development of brain inflammation and sepsis, or ameliorate the symptoms of these conditions, by restoring or maintaining normal BBB function, thereby decreasing the permeability of the BBB, preventing leukocyte extravasation.

Recent studies using an animal model of multiple sclerosis (experimental autoimmune encephalitis) suggest phospholipase A2 enzymes are involved in causing both the behavioral deficits and the inflammation that characterize MS [116]. Inhibition of the phospholipase A2 enzyme resulted in significant behavioral improvement and reduced inflammation. As a result, there is an interest in the potential ability of phospholipase A2 inhibitors in managing this debilitating disease. Cunningham and colleagues [117] have disclosed a method for monitoring the neuroinflammatory destruction of neurons related to phospholipase A2 activity. The invention describes a method for detecting inflammatory disease by detecting an increase in the activity of at least one inflammatory enzyme, and detecting the presence of at least one fragment of a nervous system-specific protein. The invention also includes a method of treating MS through the inhibition of PLA2 activity.

In terms of the role of lipids in promoting health status, there is evidence that omega-3 polyunsaturated fatty acids may have a beneficial impact, and some of that may be due

to an anti-inflammatory action. They may do this in a number of ways; one possibility is that they decrease the conversion of arachidonic acid to pro-inflammatory eicosanoids, or they may serve as alternative substrates for the 5-lipoxygenase pathway, producing less potent leukotriene mediators. One essential fatty acid that is of particular interest is eicosapentaenoic acid. This fatty acid, and analogues prepared from it, appear to have very potent anti-inflammatory actions. In terms of brain inflammation, it has been demonstrated that eicosapentaenoic acid can attenuate the behavioural changes normally induced by administration of IL-1β [118]. The potential value of drugs targeted at the receptors for eicosapentaenoic acid and its analogues has been recognized, and Serhan and colleagues [119] have patented the art for the screening of such agents.

MISCELLANEOUS APPROACHES

A number of agents have been disclosed in the patent literature that may have potential therapeutic value in terms of their anti-inflammatory actions, but the mechanisms by which they produce their effects have not been fully elucidated. Holers [120] has disclosed that lipids, annexin, and lipid-annexin complexes can block or inhibit the binding of natural antibodies to the annexin-4 or phospholipid that is expressed on the surface of a cell that is in or adjacent to a tissue that is undergoing, or is at risk of undergoing, ischemia-reperfusion injury. It is also disclosed that this therapy could be used in patients suffering diseases, such as autoimmune and inflammatory conditions, in order to prevent the damage associated with chronic and intermittent ischemia.

Hensley [121] has disclosed that lanthionine ketimine derivatives and thiomorpholine dicarboxylic acid (TMDCA) derivates may have a role in the prevention or treatment of diseases that affect the CNS, such as amyotrophic lateral sclerosis. These compounds have anti-oxidant, anti-neuroinflammatory and neuroprotective activities.

The hormone erythropoietin (EPO) is the key haematopoietic growth factor in the human body and is used extensively for the treatment of anemia. EPO may have broad neuroprotective capabilities in the CNS following injury. EPO-derived peptides comprising about 7 to about 25 amino acids, have been tested *in vitro* and *in vivo* for therapeutic efficacy. It has been shown that these EPO-derived peptides are highly protective in mouse models of multiple sclerosis (EAE), acute stroke, acute spinal cord and brain injury as well as arthritis. Yuan and colleagues [122] have disclosed that stabilized, isolated EPO-derived peptides protect against tissue damage in subjects having diverse forms of neural and non-neural organ system injury through downregulation of the inflammatory autoimmune components of these conditions.

The neural cell adhesion molecule (NCAM) plays a crucial role in development of the central nervous system regulating cell migration, differentiation and synaptogenesis. NCAM mediates cell-cell adhesion through homophilic NCAM binding, subsequently resulting in activation of the fibroblast growth factor receptor (FGFR). A synthetic peptide, FGL peptide, binds to and induces phosphorylation of FGFR without prior homophilic NCAM binding. There is evidence that FGL peptide acts neuroprotectively after an ischemic insult, both *in vitro* and *in vivo*, promoting neuronal survival after ischemic brain injury [123]. Berezin and Bock [124] have disclosed the identification of novel peptide fragments that bind to the FGFR receptor and which may be of value in the treatment of a range of different pathological CNS conditions including stroke, Parkinson's disease and Alzheimer's disease. Bock [125] has also disclosed how conjugates of a peptide ligand for the fibroblast growth factor receptor and metallothionein, may enable the targeted delivery of the ligand to the brain.

CURRENT & FUTURE DEVELOPMENTS

Improved management of acute injury to the CNS will require improved management of the underlying inflammatory processes. However, one of the problems faced is that inflammation in general, and neuroinflammation in particular, is a very complex process. This is highlighted by the many diverse approaches that are being adopted in an effort to manage neuroinflammation. At present, it is impossible to say which approach or approaches will be successful. One of the major complications is that many of the mediators of inflammation that could serve as targets for anti-inflammatory drugs, have both pro- and anti-inflammatory actions. In addition, it is not desirable to have anti-inflammatory agents that might cause severe immunosuppression. Therefore, for any drug to be effective in this area, there must be a good balance between the therapeutic efficacy and deleterious side effects. If that balance can be achieved, and an effective anti-neuroinflammatory agent produced, it will undoubtedly have substantial clinical and economic benefits. The timing of the administration of the therapeutic agents is also a critical issue. For example, there is evidence that NSAIDs may have a beneficial role in Parkinson's disease. However, the benefit derived from these agents is more likely to be observed in terms of disease prevention rather than treatment of the established condition [11]. Finally, whilst this review has primarily focused on agents which may act by inhibiting the pro-inflammatory actions of a range of inflammatory mediators, in terms of managing CNS inflammation, there is an equal potential for agents to promote or potentiate the natural anti-inflammatory actions of mediators, providing an major alternative route for the treatment of neuroinflammation [126].

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