The Potential Application of Granulocyte Colony Stimulating Factor Therapy on Neuropathic Pain

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The precise definition of the International Association for the Study of Pain (IASP) revised in 2008 states that neuropathic pain is a type of pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. This kind of pain is due to long-term dysfunction of the nervous system and is clinically characterized by spontaneous and evoked types of chronic pain, which are involved by various distinct pathophysiological mechanisms in the peripheral and central nervous systems. It is relatively common, with an incidence estimated at 0.6% to 1.5% in the US population. Unfortunately, there was no effective therapy until recently. Our research team found an effective strategy in treating neuropathic pain that resulted from interactions between leukocyte-derived opioid peptides and their receptors on peripheral sensory neurons. Here, we briefly review granulocyte colony stimulating factor (G-CSF) therapy in an animal model of neuropathic pain. Our studies also proved that G-CSF can increase the number of opioid-contained polymorphonuclear cells and significantly relieve neuropathic pain. These studies have led to an increased understanding of the opioids and cytokines -modulating peripheral analgesia effect on neuropathic pain, which opens a new avenue in its treatment. *(Chang Gung Med J 2009;32:235-46)*

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The prevalence of neuropathic pain is expected to exceed 75 million cases worldwide by 2010. Only 15-30% of neuropathic pain is treatable using the most potent existing pain relievers - morphine and other opioids.[1] As the mean age of the population rises, the incidence of chronic diseases such as diabetes, cardiovascular disease, and rheumatoid arthritis are expected to skyrocket; thus, better analgesics are urgently needed. Under normal conditions, nociceptive responses correlate well with tissue damage and subsequent inflammation. However, some changes may occur which move the function of the system more toward the neuropathic end. These changes are promoted by variations in the quantity and quality of noxious input that distort the function of the pain sensory system. The result is that pain

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loses its protective aspect and becomes the problem itself.[2]

Recently, it has become clear that inflammatory and immune mechanisms both in the peripheral and the central nervous system play an important role in neuropathic pain. When tissue damage occurs, an inflammatory response develops, triggered by various proinflammatory and pro-algesic mediators activating specialized peripheral pain signaling sensory neurons. The peripheral terminals of Aδ and C fibers transduce and propagate noxious stimuli from peripheral tissues (such as skin, muscles, joints, and viscera) to the dorsal horn of the spinal cord and thereafter to the brain. At spinal and supraspinal sites, the integration of signals from pro-algesic neurotransmitters, environmental and cognitive factors eventually results in the sensation of pain.[3]

However, neural fibers sprouting after nerve injury will discharge unusually due to increased sodium channels and ectopic discharges.[4] Peripheral and central sensitization is also involved.[5] Some cytokines like tumor necrosis factor (TNF) -α or interleukin (IL)-1β are proinflammatory substances and induce inflammation and increase neuropathic pain.[6] Symptoms and signs of neuropathic pain include allodynia, hyperaglesia and spontaneous pain.[7] On the contrary, there are endogenous mechanisms that counteract pain development. These mechanisms in the brain and spinal cord are well described and consist of descending pain inhibitory pathways, which contain mostly opioid peptides, noradrenaline and serotonin, and their receptors.[8]

Over the last three decades, considerable advances have been made in the understanding the role of the opioid peptide systems in chronic pain.[9] Recent interest has focused on the characterization of opioid receptors on nociceptors because their activation can inhibit pain directly at its origin without unwanted central side effects.[1]

A polymorphonuclear cell (PMN) is a kind of granulocyte which can secrete opioid peptides.[10] G-CSF can stimulate bone marrow to produce numerous PMN cells.[11] Although the underlying mechanisms are incompletely understood, G-CSF can modulate cytokines,[12] chemokines[13] and CD34+ adhesion molecules to affect pain transmission.[14] The above findings indicate that G-CSF may play a role in indirect or direct pain inhibition and is a potential mediator in controlling pain. Also, research on G-CSF may provide new insights into intrinsic mechanisms of pain control and develop new strategies and alternative approaches to treat pain.

Animal models of neuropathic pain

The first widely used animal model of neuropathic pain was chronic constriction injury (CCI) of the rat sciatic nerve,[7] in which the sciatic nerve was loosely tied with four ligatures of chromic gut at mid-thigh level. The rats then engaged in protective behavior and had lowered thresholds to heat, cooling, and mechanical stimuli. Subsequent work indicated that an immune-mediated response to the chromic suture played a major role in the development of neuropathic pain.[15] The nerve swelled, leading to nerve compression and axotomy, and an axotomy by itself induced pain. This CCI model in the rat led to neuropathic pain symptoms including hyperalgesia, allodynia and apparent spontaneous pain that began in about two days and lasted for 2-3 months.[7,16]

Other widely used animal models include partial sciatic nerve ligation[17] and spinal nerve ligation models.[18] Research on these animal models of peripheral neuropathic pain (the pain syndrome resulting from lesions of the peripheral nervous system) has made it clear that a number of mechanisms are involved, including ectopic excitability of sensory neurons, altered gene expression of sensory neurons and sensitization of neurons in the dorsal horn of the spinal cord.[19]

Trauma has not been the only model used in studies of neuropathic pain. One of the leading causes of pain in humans is diabetic neuropathy. Injection of streptozotocin leads to an animal model of diabetes and is associated with the development of neuropathy similar to what is seen in humans. Hyperalgesia can be measured in rodent models, thus providing a means to study treatments and mechanisms of pain in this neuropathy model.[20]

Neuropathic pain models were first described in rats;[7] there is a translation of these models to mice. This is fundamental for a transgenic approach to neuropathic pain treatment.

Inflammation increases neuropathic pain

Once tissue has been damaged mechanically or by infection, ischemia, tumor growth or an autoimmune process, infiltration of inflammatory cells, as

well as activation of resident immune cells, leads to subsequent production and secretion of various inflammatory mediators. These mediators include proinflammatory cytokines, chemokines and amines.[19,21] The expression of these mediators increases and promotes neuroimmune activation when neuropathic pain persists.

Injury of a peripheral nerve initiates an inflammatory cascade in which mast cells residing in the nerve are the first to be activated.[22] These cells release mediators such as histamine and TNF,[22,23] which sensitize nociceptors and contribute to the recruitment of neutrophils and macrophages. Mediators released by neutrophils (including the chemokine MIP-1α and the cytokine IL-1β) assist in the recruitment of macrophages.[24,25] Both neutrophils and macrophages in the nerve produce and secrete mediators such as TNF and prostaglandin E2 (PGE2) that can further sensitize nociceptors.[26,27] Nerve injury also initiates Schwann cell de-differentiation and the release of several algesic mediators such as pro-inflammatory cytokines, nerve growth factor (NGF), PGE2 and ATP. These initial events promote the recruitment of T cells, which can secrete a variety of cytokines depending on their subtypes. This cocktail of mediators serves as a mechanism for enhanced inflammatory response in the injured nerve and contributes to neuropathic pain.

Cytokines in peripheral nerves have been mostly localized to Schwann cells or macrophages, and occasionally to fibroblasts. In dorsal root ganglion (DRG) neurons, not only are cytokine levels increased after nerve injury,[28] but there is also a phenotypic switch leading to TNFα expression in a population of medium size DRG neurons,[29] indicating a possible alteration in the function of these neurons. Increases in cytokine expression have also been found in the lumbar spinal cord after CCI and in other partial nerve injury models[30] as well as in particular regions of the central nerve system (CNS) such as the hippocampus.[6]

The involvement of glial cells, principally microglia and astrocytes, in pain processing has been increasingly established by many laboratories using varied techniques and animal models of transient and persistent pain. When glia become activated, they begin to release a variety of chemical substances that amplify the pain message, thus causing hyperalgesia.[31] Recent studies suggested that microglia are more important for the initiation, while astrocytes were more important for maintenance of neuropathic pain.[32] First, spinal cord glia cells are activated in response to trauma or inflammation of peripheral nerves, resulting in neuropathic pain.[33] This is reflected by increased expression of activation markers, including glial fibrillary acidic protein by astrocytes and complement-type-3 receptors by microglia. Second, glial activation drives neuropathic pain, since blockade of glial activation prevents and/or reverses it. Third, nerve injury downregulates glial glutamate transporters in the spinal cord dorsal horn, which increases the excitability of pain-transmission neurons by increasing extracellular glutamate levels.[34] Fourth, neuropathy causes spinal cord glial cells to enhance pain release neuroexcitatory glial proinflammatory cytokines (TNF, IL-1 and IL-6).[33] Fifth, the pain enhancing effects of neuropathy are mimicked by spinal cord glial activation in the absence of peripheral nerve injury[35] but with perispinal (intrathecal) delivery of proinflammatory cytokines.[36]

The implications of these studies are clear. Spinal cord glia are sensitive to and activated by many perturbations. Activation can occur in response to peripheral or central inflammation or infection, in response to peripheral injury as occurs in neuropathy, or in response to drugs such as morphine. Whether glia cells are activated in their role as immune-like cells in response to neuron-to-glia signals or in response to morphine, the end result is strikingly similar. That is, activated glia cells begin producing and releasing a host of neuroexcitatory substances.

Opioid-induced glial activation contributes to modulation of neuropatheic pain

Traditionally, glia cells (astrocytes and microglia) were viewed as structural supports for neurons and important for maintaining CNS homeostasis. Glia cells were long overlooked in pain research due to their lack of axons and their yet-to-be-discovered roles in cell-to-cell communication.[37] While the roles of CNS glia in providing immune surveillance, clearance of debris, and regulation of the ionic and chemical composition of the extracellular space have been acknowledged as pivotal to host survival, the actions of glia in variable pain states has only attracted the attention of pain researchers since the early 1990s.[38]

Opioid-induced glial activation also undermines opioid-induced pain suppression. It is now clear from recent studies that glia do indeed compromise the ability of opioids to suppress pain.[39] Glia cells now have a well-established role in initiating and maintaining increased nociception in response to peripheral nerve injury. More recently, several laboratories have documented that glia can powerfully modulate the analgesic actions of chronically administered opioids.[40] Preventing opioid activation of glia may well be a clinically relevant strategy for increasing opioid analgesia while decreasing the negative consequences of repeated opioid use.[41]

Leukocyte-derived opioid peptides and inhibition of pain

When peripheral nerve injury occurs, the synapses secrete substance P to transfer the noxious signal to the CNS, and then induce pain.[42] In addition, some cytokines, like TNF-α, IL-1β and IL-6, express largely during the early period of inflammation.[43] However, it is less well known if immune cells also produce mediators that can effectively counteract pain. Several peripheral endogenous antinociceptive mechanisms are involved in counteracting inflammatory hyperalgesia. Most of these involve the release of opioid peptides, endocannabinoids, somatostatin, or anti-inflammatory cytokines.[44]

Endogenous peripheral analgesia contributes to postoperative pain control.[45] This analgesic effect was demonstrated immediately following an operative procedure, showing the importance of early inflammatory pain control in humans. Furthermore, in an animal model of Freund's complete adjuvant (FCA)-induced inflammation, opioid-mediated endogenous peripheral analgesia measured by a paw pressure test was significantly less efficacious in early than in late inflammation (2 vs. 96 h post intraplantar injection of FCA, respectively).[46]

One of the effects of opioid peptides is reduction of substance P secreted by primary afferent nerves. Then, the noxious signal transfer pathway is blocked.[9] Under inflammatory conditions, leukocytes secrete opioid peptides, which bind to opioid receptors on peripheral sensory neurons and mediate antinociception.[47]

Two endogenous opioid peptides, β-endorphin (END) and enkephalin (ENK), seem to be primarily responsible for this intrinsic analgesia. END and ENK are detectable by immunohistochemistry in various immune cells of the inflamed paw including monocytes, lymphocytes, and granulocytes.[48] Opioid peptides have been quantified in immune cells by radioimmunoassay,[49,50] and their opioid peptide precursor messenger RNAs, proopiomelanocortin and proenkephalin mRNA, are detectable in inflamed tissue.[49] The relevance of immune cells in the generation of peripheral stress-induced analgesia is supported by studies using total-body irradiation and cyclosporine A. Both treatments induce immunosuppression and abolish stress-induced endogenous opioid analgesia.[49,51]

The opioid peptides are also secreted by stressful stimuli, such as local injection of corticotropin releasing factor, and the corresponding receptors are present on opioid-expressing leukocytes.[52] Clinically, opioid peptides are present in inflamed synovial tissue and can inhibit pain after knee surgery through an action specific to intra-articular opioid receptors.[45]

Opioids and their receptors on peripheral sensory neurons

The main groups of opioid peptides, enkephalins, dynorphins and β-endorphin, are derived from three different precursor proteins, proenkephalin, prodynorphin, and proopiomelanocortin, respectively.[53-55] Numerous leukocytes, including lymphocytes, macrophages, monocytes, and human peripheral blood mononuclear cells, have been reported to contain these opioid peptides.[56,57] Opioids are the most powerful drugs for severe acute and chronic pain, but their widespread use is hampered by side effects from CNS receptor activation which leads to respiratory depression, nausea, clouding of the consciousness, constipation, addiction and tolerance.[58]

Three types of opioid receptors (ORs) μ (MOR), δ (DOR) and κ (KOR) encoded by three respective genes were identified in the early 1990s.[58] ORs play an important role in pain inhibition, and the endogenous peripheral antinociception in early inflammation is not limited by the number of opioid-containing leukocytes but by OR expression.[59] Opioid receptors are widely and differentially distributed in the CNS, spinal cord and nonneuronal tissues. MOR, in particular, is widely distributed throughout the

forebrain, midbrain, and hindbrain with greatest expression apparent in the neocortex, caudateputamen, nucleus accumbens, thalamus, hippocampus, amygdala, and nucleus tractus solitarius.[60] MOR expression has also been confirmed in the DRG, spinal cord, and trigeminal nucleus of the ascending pain pathway as well as the central gray area, pontine, gigantocellulare, and intermediate reticular nuclei of the descending pain pathway, with predominantly MOR and KOR expression in the median raphe and raphe magnus.[61] All three receptors can mediate pain inhibition, and these receptors have been found on cell bodies in the DRG and on the peripheral terminals of primary afferent neurons in animals[62] and humans.[63]

These three opioid receptors belong to the family of seven transmembrane G-protein coupled receptors, and share extensive structural homology. Modification of Ca^{2+} and K^{+} conductance by opioid receptors can lead to a decrease in neuronal excitability, a decrease in the neuronal firing rate, and inhibition of neurotransmitter release.[64,65] Functionally, opioid receptors have been implicated in regulation of pain, reinforcement, rewarding, neuroendocrine modulation, and alteration in neurotransmitter release.[61] Inflammation-induced enhancement of opioid antinociceptive potency is characteristic predominantly for MOR.[9] Inflammation of peripheral tissues also leads to increased synthesis in DRG neurons and to axonal transport of opioid receptors, resulting in their up-regulation and enhanced G-protein coupling at peripheral nerve terminals.[66] However, down-regulation of MOR has been documented both pre- and post-synaptically after nerve injury[67] and could result in stimulus-evoked pain hypersenitivity. In early inflammatory stages (6 h), all three families of opioid peptides and opioid receptors are involved, and at later stages (4-6 days), β-endorphin, acting at MOR and DOR, are dominant.

The approaches through endogenous peripheral antinociception that bypass the activating CNS ORs seems to provide a better way to control neuropathic pain. Enhancement of the potency of MOR agonists during inflammation could arise from the changes occurring in opioid receptors, predominantly in the affinity or number of MORs. Perspective therapeutic strategies might aim towards increasing opioid receptor availability or efficacy of OR signal transduction.

Biological function of G-CSF

Since the infancy of the use of opium poppy extracts to treat pain around 3500 BC, the search for treatments that provide effective relief from acute and chronic pain has continued to grow at an extraordinary rate. G-CSF was identified initially as a glycoprotein growth factor for neutrophils.[68] Human G-CSF is encoded by a single gene located on chromosome 17 q11-22 and is produced mainly in cells of monocyte/macrophage origin.[68] The production of G-CSF protein is not constitutive, and it can be induced by a wide variety of stimulatory agents including lipopolysaccharide (LPS), TNF-α, IL-1β and IFN-γ.[69]

G-CSF is also a key hemopoietic factor of the myeloid lineage, and has been extensively used for more than 10 years in the treatment of neutropenia as well as for bone marrow reconstitution and stem cell mobilization.[70] Because of their potency and lack of serious toxicity, G-CSF-mobilized peripheral blood stem and progenitor cells (PBSCs) are now replacing marrow-derived hematopoietic progenitors cells as a stem cell source.[71] Doses of 3-5 mg/kg/day result in less efficient PBSC mobilization, and high doses of 16-24 mg/kg/day may not be cost-effective and may be associated with increased toxicity. The optimal dose of G-CSF treatment for PBSC mobilization is 10 μg/kg/day.[72]

G-CSF is a particular growth factor that could encourage the bone marrow (BM) to produce more granulocytes.[11] The mobilization of neutrophils into the circulation is a complex cascade that involves a coalition of proteases, chemokines/cytokines and adhesion molecules.[73] Moreover, administration of G-CSF with other growth factors dramatically increases the amount of BM-derived neuronal cells released into the circulation. Treatment with both G-CSF and GM-CSF can produce more new white blood cells than treatment with G-CSF alone to enhance the immune system of cancer patients.[74] In one study, G-CSF and stem cell factor administration in mice resulted in more than a 200-fold increase in the pluripotent hematopoietic stem cell population.[75]

G-CSF acts by binding to its receptor (G-CSFR), a member of the class I cytokine receptor family expressed in various hemopoietic cells such as stem cells, multipotent progenitors, myeloid com-

mitted progenitors, neutrophils, and monocytes.[76] The presence of G-CSFRs is not only restricted to myeloid cells, although the biologic effects of G-CSFR expression in nonmyeloid tissues remain uncertain. Several investigators have reported the presence of G-CSFRs in subsets of monocytes and lymphoid cells, platelets, vascular endothelial cells, human placenta, trophoblastic cells, and possibly neurons and glial cells as well.[77]

The mechanisms involved in the analgesic effect of G-CSF

How does G-CSF modulate neuropathic pain? We hypothesize that G-CSF produces an analgesic effect based on two major biological and molecular functions. First, G-CSF can increase the number of hematopoietic stem cells by stimulating bone marrow proliferation, and prompt the differentiation of white blood cells (WBC) from hematopoietic stem cells, especially into PMNs.[11,75] PMNs are the major leukocyte (60%-70%) with an opioid-containing population in an inflamed lesion during early inflammation.[10] Our studies showed that circulating WBC and PMN cells in CCI rats were significantly increased with a single G-CSF treatment (Fig. 1). Several studies support the idea that endogenous opioid-mediated peripheral analgesia contributes to significant pain relief.[46,78] To enhance the opioid-mediated peripheral analgesia effect, we successfully applied exogenous G-CSF to attenuate the development of thermal hyperalgesia in CCI rats (Fig. 2), and in a subsequent study confirmed that G-CSF enhanced the opioid-mediated peripheral analgesic effects through recruitment of opioid-containing PMN cells to the injured nerve (to be published). The above studies suggest that opioid-containing PMN cells play an important role in peripheral analgesia after G-CSF administration.

Neutrophilic granulocytes play a major role in the inflammatory response, resulting in tissue damage. Therefore, the indications for G-CSF in combating infectious diseases seem to be limited because of fears about their proinflammatory activity. In contrast to these concerns, G-CSF has proven itself to be an anti-inflammatory immunomodulator. Animal, volunteer, and patient studies have all shown that G-CSF reduces inflammatory activity by inhibiting the production or activity of the main inflammatory mediators IL-1β, TNF-α, IFN-γ[79,80] and IL-6 in our

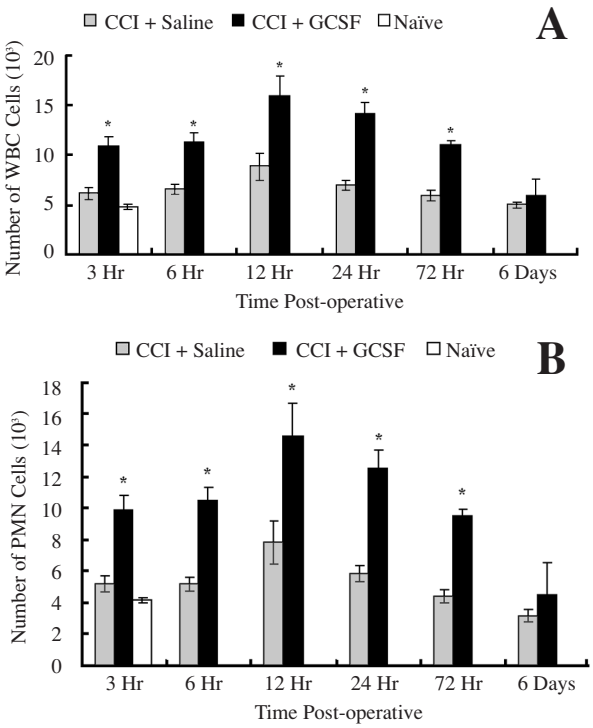

Fig. 1 The effects of G-CSF on the number of circulating WBC and PMNs. (A) Rats (n = 7) were intravenously injected with vehicle (saline + CCI) *(gray bar)* or with G-CSF (GCSF + CCI) *(black bar)* at different time points; naïve rats are represented by the white bar. Immune cell sub-populations in the circulating blood were quantified by counting blood cells. Circulating WBCs were significantly increased at 3, 6, 12, 24 and 72 hours ($*p < 0.05$, Mann-Whitney test). (B) Circulating PMNs were significantly increased at 3, 6, 12, 24 and 72 hours, ($*p < 0.05$, Mann-Whitney test).

study. Thus, the modulation effects of G-CSF on cytokine responses and networks implicate another pain-inhibition pathway (Fig. 3). Furthermore, G-CSF has been used as an anti-inflammatory agent in murine endotoxemia.[81] Exogenous G-CSF rapidly stimulates IL-1ra production[82,83] and counteracts IL-1-mediated inflammatory cascades.[84] On the other hand, G-CSF might activate T cell immunomodulatory genes, e.g., *GATA-3* and *Stat5*, and directly inhibit proinflammatory cytokine production by T cells at pharmacologic doses.[84]

G-CSF also appears to have a direct effect on $CD4^+$ lymphocytes to increase anti-inflammatory cytokine IL-4 expression.[12] Monocytes from G-CSF-treated healthy subjects produce more IL-10 than

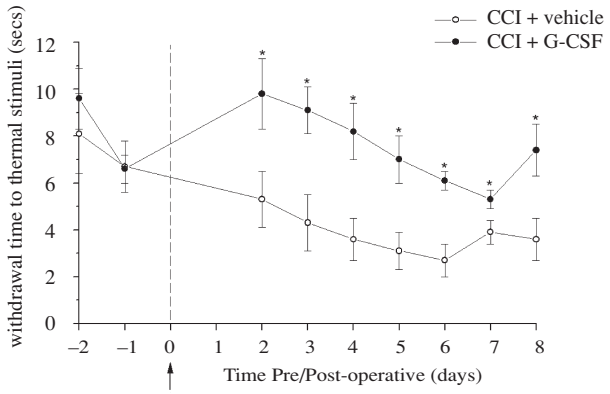

Fig. 2 G-CSF attenuates the development of thermal hyperalgesia in rats with CCI. The hyperalgesic index represents alterations in thermal sensitivity in CCI rats with or without G-CSF intravenous injection during an 8-day experimental period. Thermal hyperalgesia significantly developed compared with that of pre-operation levels and persisted during the experimental period in CCI rats with vehicle injection (n = 6); In contrast, injection of G-CSF significantly attenuated the development of thermal hyperalgesia from 2 to 8 days after operation, compared with that of vehicle ($^*p < 0.05$, repeated measures ANOVA, n = 6).

unmobilized monocytes in response to LPS.[85] We conclude that the cytokine cascade of inflammatory mediators could thus be interrupted to a great extent after G-CSF treatment-induced cytokine modulation, leading to an analgesic effect.

These findings on G-CSF, including our own, provide new insights into the intrinsic mechanisms of pain control. It can not only alleviate neuropathic pain but also repair lesion sites which are damaged mechanically or by infection, ischemia, tumor growth or an autoimmune process. Moreover, the G-CSF mediated analgesic effect systemically modulates the immune system rather than blocking a single neuropathic pain-arising pathway. This modulation forms a perfect new balance after an abnormal stimulus caused by nerve injury, and may eliminate side effects caused by an imbalance of immune mediators. However, in patients, one or more of the following signs and symptoms such as dyspnea, chest pain, nausea, hypoxemia, diaphoresis anaphylaxis, syncope and flushing were observed shortly after subcutaneous injection of G-CSF.[86] Predictive

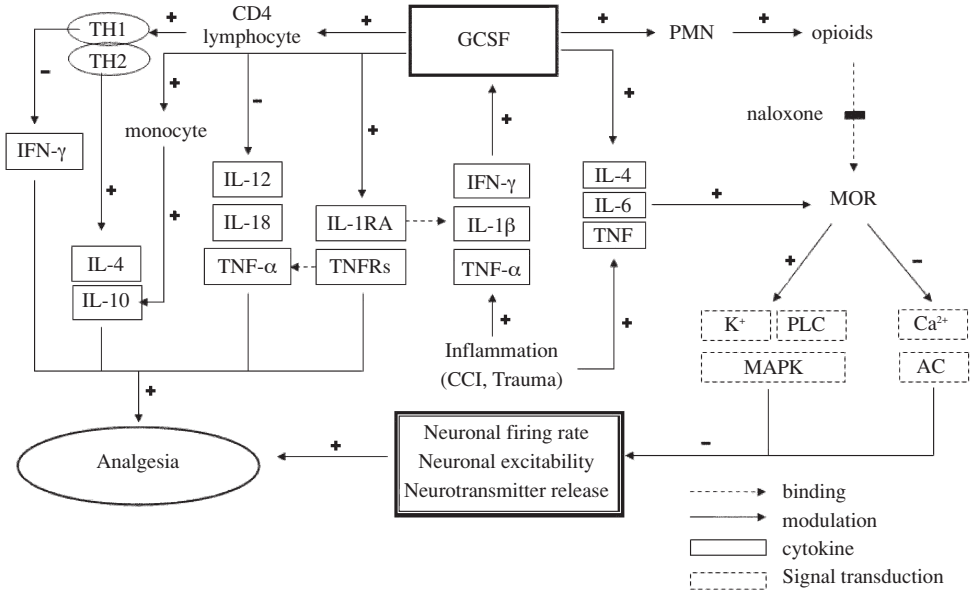

Fig. 3 Proposed models for G-CSF mediated peripheral analgesia at a late stage of inflammation. G-CSF enhances the release of IL-1 receptor antagonist (IL-1RA) and TNF receptors (TNFRs). G-CSF also appears to have a direct effect on $CD4^+$ lymphocytes to increase anti-inflammatory cytokine IL-4 expression. Monocytes from G-CSF-treated healthy subjects produce more IL-10 than unmobilized monocytes in response to lipopolysaccharide (LPS). The inflammatory mediator interleukin-6 (IL-6), interleukin-4 (IL-4) and tumor necrosis factor (TNF) induce μ opioid receptor (MOR) expression. Opioid receptors (ORs) indirectly activate phospholipase C (PLC), the mitogen-activated protein kinase (MAPK) cascade and inhibit adenylyl cyclase (AC) by another intermediary messenger system. Modification of Ca^{2+} and K^+ conductance by ORs can lead to a decrease in neuronal excitability, a decrease in the neuronal firing rate, and inhibition of neurotransmitter release.

factors could not be identified, and the underlying mechanism leading to these reactions is unknown.

Conclusions

Current clinical treatments for chronic pain target the peripheral nerve system with only limited success.[87] However, increasing evidence from G-CSF treatment shows a significant analgesic effect on chronic pain. According to the results of our study, we found that a single administration of G-CSF attenuated allodynia and hyperalgesia in rats with CCI and this pain alleviation effect lasted for at least 30 days (data not shown). Moreover, G-CSF only increases the proliferation of PMN cells and has no side effects on other blood cells (to be published). G-CSF has a full effect on alleviating thermal hyperalgesia and mechanical allodynia before neuropathic pain is completely established. Otherwise, it has only a partial or no effect on alleviating neuropathic pain.[88]

Until a so-called miracle treatment is found, it is obvious that more research is needed in both basic and clinical applications for chronic pain control. Scientists must examine receptors, proteins, and neurotransmitters at the cellular and molecular levels to determine their effects on neuropathic processes. G-CSF therapy has proved to be an innovative strategy and alternative approach in neuropathic pain treatment.

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顆粒球生長激素療法對神經病變痛具有潛力的臨床應用

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根據國際疼痛研究學會 (IASP) 在 2008 年修正過的最新定義，神經病變痛是一種起因於體感覺系統直接受到損害或疾病影響的結果。這種形式的疼痛是由於長期的神經系統功能障礙以及臨床上具有自然發生的慢性疼痛特徵，這涉及了許多的中樞及周邊神經各種特定變化的病理機制。神經病變痛非常普遍存在，據估計在美國有 0.6% 到 1.5% 的人口受到影響。不幸的是，目前仍無特別有效之治療方法。我們研究團隊最近發現一種對神經病變痛有效的治療方式，可經由周邊感覺神經元中的白血球衍生的類鴉片胜肽及其受器的交互作用獲得。本文中將簡短地回顧以動物模式進行的顆粒球生長激素療法在神經病變痛方面的效果，我們的研究也佐證了顆粒球生長激素的確刺激了能分泌類鴉片胜肽之多型核細胞的數量，並顯著改善神經病變痛的程度，這些研究不但爲我們帶來了更多類鴉片胜肽及細胞激素對神經病變痛的調節及止痛效果的了解，也打開了一條通往治療神經病變痛的康莊大道。(長庚醫誌 2009;32:235-46)

關鍵詞：顆粒球生長激素療法、神經病變痛、發炎反應、多型核細胞、類鴉片胜肽、細胞激素

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