Calcitonin Gene–Related Peptide and Thermal Injury: Review of Literature

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The aim of this review article is to report about the anti-inflammatory properties of calcitonin gene–related peptide (CGRP) in burns. CGRP is a 37-amino acid neuropeptide, primarily released from sensory nerves and is well known as the most potent and long-lasting microvascular vasodilator in vitro and hypotensive agents in vivo. A wide range of proinflammatory stimuli can induce the release of neuropeptides from cutaneous sensory nerves, including heat, physical trauma, UV radiation, and irritant chemicals. These proinflammatory stimuli are known to induce the release of CGRP from cutaneous sensory nerves. The anti-inflammatory effects of CGRP in a range of species and in human clinical conditions are detailed, and potential therapeutic applications based on the use of antagonists and gene targeting of agonists are discussed.

Thermal injury of the skin results in local tissue destruction and a systemic response. The increased temperature kills cells in the immediate area and denatures the surrounding extracellular matrix proteins. Earlier experimental investigations have shown that the inflammatory reaction is divided into early and delayed phases. The first phase is believed to be due to the direct effect of heat on burned tissue causing an increased capillary filtration followed by edema formation. The second, or delayed phase, depends on a cascade of mediators released by the local tissue and central nervous system, leading to physiological changes including increased capillary hydrostatic pressure, leakage of intravascular fluid and proteins into the interstitium, decreased cardiac output, and suppression of the immune system. This delayed reaction is induced by the contribution of sensory neuropeptides such as calcitonin gene–related peptide (CGRP).

CGRP is a 37-amino acid neuropeptide encoded by an alternative processing of the calcitonin gene in thyroid C cells. It is found in sensory peptidergic nerves that are present...
**Figure 1.** Relevance of calcitonin gene related peptide. Action in tissue repair.

in most tissues and organ systems, including blood vessels, heart, kidney, gastrointestinal system, and lymphoid organs. CGRP is well known as a potent and long-lasting microvascular vasodilator in vitro and a hypotensive agent in vivo.⁵⁻¹¹

CGRP can potentiate inflammatory edema in skin induced by mediators that increase microvascular permeability.⁵ This is thought to be a consequence of its action as a microvascular vasodilator.

CGRP has a proliferative effect on human endothelial cells; therefore, it is important for the formation of new vessels, for example, in ischemia, inflammation, and the healing of wounds; it is also regarded as an important modulator of the inflammatory response after the activation of sensory nerves (Fig 1).²,¹² The aim of this review article is to report the anti-inflammatory properties of CGRP in burns.

**BURN PATHOPHYSIOLOGY**

Several investigations have focused on the circulatory and microcirculatory alterations associated with burn shock and edema formation in both burned and nonburned tissues.

Under normal physiological conditions, blood pressure in the capillaries causes the filtration of fluid into the interstitial space. The thermal injury causes extravasation of plasma into the burn wound and the surrounding tissues. Edema develops when the filtration rate exceeds the flow in the lymphatic vessels draining the same tissue. It follows a biphasic pattern. An immediate increase in water is seen in the first hour after injury. A second phase, which is more gradual, occurs 12 to 24 hours after burn injury.¹³ Thermal injury causes direct and indirect mediator-modulated changes of the permeability of blood tissue barrier of the capillaries and venules. This pathophysiological response involves several classes of chemical mediators¹⁴ interacting in a complex manner to cause the pain and secondary tissue damage (Table 1).
**Table 1. Inflammatory mediators of burn**

| Mediators                          | Effects                                | Tissue effect                                      | References |
|------------------------------------|----------------------------------------|---------------------------------------------------|------------|
| Histamine                          | ↓ Blood pressure                       | Arteriolar dilation and venular constriction      | 15–18      |
|                                    | Hypovolemia                            |                                                   |            |
| Prostaglandin E₂                   | ↓ Systemic arterial and pulmonary arterial blood pressure | Vasodilation                                      | 19, 20     |
| Leukotriene B₄                     | Pulmonary hypertension                 | ↑ Permeability                                     | 21         |
| Leukotriene D₄                     | Pulmonary hypertension                 | ↑ Permeability                                     | 21         |
| Tromboxane A₂                      | GI* ischemia                           | Vasoconstriction of pulmonary vessels             | 19, 22–24  |
| Tromboxane B₂                      | Pulmonary hypertension                 | ↑ Permeability                                     | 21, 25     |
| Bradykinin                         | ↓ Blood pressure                       |                                                   |            |
|                                    | Hypovolemia                            | ↑ Permeability                                     | 18         |
| Serotonin                          | ↑ Heart rate                           | Vasoconstriction (α receptors)                    | 17, 21, 26 |
|                                    | ↑ Blood pressure                       |                                                   |            |
|                                    | ↑ Metabolism                           |                                                   |            |
| Catecholamine                      | Cardiac dysfunction                    | Tissue damage                                      | 15, 16, 21, 27 |
| Oxygen radicals                    |                                        | ↑ Permeability                                     |            |
| Platelet aggregation factor        | ↑ Blood pressure                       | Vasoconstriction                                   | 28–30      |
| Angiotensin II                     | GI ischemia                            | Vasoconstriction                                   | 31         |
| Vasopressin                        | GI ischemia                            | Vasoconstriction                                   | 32         |
| Procalcitonin                      | ↑ Blood pressure                       |                                                   | 33, 34     |
| Antimicrobial peptides (defensins and cathelicidins) | Protective role against microbes | | 35–37 |
| Tachykinins                        | Edema                                  | Vasoconstriction                                   | 38–43      |
| Substance P                        |                                        | ↑ Permeability                                     |            |
| Neurokinin A                       |                                        |                                                   |            |
| Neurokinin B                       |                                        |                                                   |            |
| Calcitonin gene–related peptide    | ↑ Heart rate                           | Vasoconstriction                                   | 38, 44     |
|                                    | ↓ Blood pressure                       | ↑ Permeability                                     |            |
|                                    |                                        | Proliferative effect on human endothelium         |            |

*GI indicates gastrointestinal.

**SENSORY NERVOUS SYSTEM AND INFLAMMATION**

There is evidence that the activation of the peripheral nervous system generates the major features of inflammation. The so-called “neurogenic inflammation” is mainly due to the activation of C-fibers\(^{45}\) and Aδ-fibers,\(^{46, 47}\) leading to erythema, wheal, and flare.\(^{48}\)
It is also accepted that these symptoms are due to antidromic release of sensory neuropeptides, in which tachykinins, such as substance P (SP), neurokinin (NK) A, and NKB together with CGRP, play a major role.\textsuperscript{48–54}

The neurogenic inflammatory response is complex and cannot simply be regarded as a series of neuronal events occurring in isolation. Indeed, it is known that the initiation and sustenance of neurogenic inflammation depend on a variety of factors, such as endothelium, kininogens, and neuropeptides, present in the local environment. The vasodilation response characteristic of neurogenic inflammation requires the presence of endothelium and is linked to the production of nitric oxide (NO).\textsuperscript{55} It has been suggested that NO may act prejunctionally or within peripheral neurons to mediate the release of neuropeptides during neurogenic inflammation within the skin microvasculature.\textsuperscript{56,57} In the course of inflammation, ubiquitous kininogens, including bradykinin, are important mediators of inflammation. In addition to direct activation and sensitization of nociceptors, there is evidence that kinins are proinflammatory, leading to vasodilation, plasma extravasation, and the release of other inflammatory mediators, notably the neuropeptides SP and CGRP.\textsuperscript{58} The finding that the pungent extract of the Hungarian pepper, capsaicin (8-methyl-\textit{N}-vanillyl-6-noneamide), can be used as a neurotoxin for the nonmyelinated sensory afferents\textsuperscript{59} is of crucial importance to research on the role of the nervous system in the inflammatory process. Capsaicin is selective for the stimulation and blockage of a subset of mammalian afferent neurons of dorsal root ganglia with C- and A\textdelta-fibers. In response to stimulation, peptide mediators are released from the central and peripheral nerve endings of these neurons, and both SP and CGRP are involved in the capsaicin-induced reaction. SP induces a short-lasting endothelium-dependent vasodilation through the activation of the NKI receptor,\textsuperscript{60} which is partly dependent on NO release.\textsuperscript{61} SP also causes plasma protein extravasation\textsuperscript{62,63} and a concomitant histamine release from mast cells.\textsuperscript{64–67}

The most prominent features of the neurogenic inflammation are vasodilation. CGRP, most often co-released with SP, is the most potent endogenous vasodilator found in animals and humans\textsuperscript{5,68} and the most abundant neuropeptide in the peripheral nervous system.

**CALCITONIN GENE–RELATED PEPTIDE**

CGRP was identified in 1982 when Rosenfeld et al\textsuperscript{4} showed that alternative RNA processing of the calcitonin gene generated mRNAs encoding a peptide they named CGRP. It is highly expressed in certain nerves and is now known to belong to a family that includes the more recently discovered peptides adrenomedullin and amylin. This group belongs to a larger family of peptides that includes calcitonin. Calcitonin is a potent inhibitor of bone resorption, acting via receptor-mediated inhibition of osteoclast function.\textsuperscript{69} The overall effect of CGRP on bone resorption is unclear, although it can inhibit osteoclast activity,\textsuperscript{70} but it is best known for its potent cardiovascular effects.\textsuperscript{71} CGRP is distributed throughout the central and peripheral nervous systems and exhibits a range of biological effects on tissues including those associated with gastrointestinal, respiratory, endocrine, and central nervous systems (Fig 2).\textsuperscript{63,72–78}
Figure 2. The CGRP gene is expressed in the dorsal root ganglion (DRG) and is upregulated by factors that include nerve growth factor (NGF) and tissue inflammation. CGRP is released from nerves in response to several stimuli, such as capsaicin and low pH, proteinase-activated receptor (PAR activation), and mediators (e.g., kinins and prostaglandins [PG]). Opioids can inhibit the release of CGRP. The response to CGRP is inhibited by CGRP receptor antagonists.

Vascular system

CGRP is a potent arterial and venous vasodilator and is frequently co-localized with SP. Indeed, SP regulates the vasodilator activity of CGRP, suggesting that there is an important functional significance to this co-localization. There are several mechanisms by which CGRP produces vascular relaxation, as discussed in earlier reviews. It is accepted that vasodilation is mediated via the CGRP1 receptor and blocked in a competitive manner by CGRP8–37. Depending on species and blood vessel type, the vasodilating properties of CGRP can be endothelium dependent or independent, both cases involving an intracellular increase in cAMP. In this signaling system, cAMP acts as a second messenger, subsequently activating cAMP-dependent kinase and ultimately regulating ion channels, enzyme activity, and/or structural proteins.

Inflammation

A wide range of proinflammatory stimuli can induce the release of neuropeptides from cutaneous sensory nerves, including heat, physical trauma, ultraviolet radiation, and irritant chemicals. The release of these neuropeptides leads to neurogenic inflammation with erythema and edema. CGRP is considered to be an important modulator of the inflammatory...
response after the activation of sensory nerves. The action of CGRP on edema formation has been extensively studied, and interestingly, CGRP-like immunoreactivity (CGRP-LI) around blood vessels increases in chronic inflammation. In a series of studies, a potentiating action of CGRP in edema formation was demonstrated, but only when CGRP and SP were administered concomitantly. Probably, CGRP’s potentiating action is due to its induced vasodilation and not due to its direct effect. The role of CGRP in mast cell degranulation and histamine release has also been studied. The close anatomical relationship between mast cells and sensory nerves in many organs suggests that there is a physiological interaction between these two cell types. However, the capability of CGRP for the activation of mast cells is less pronounced than that of SP. In fact, CGRP has been reported to release little or no histamine.

**Wound healing**

It has been postulated that sensory neuropeptides in general act as local growth factors. There is also increasing evidence that neuropeptides participate in many of the inflammatory processes that are crucial for normal wound healing. Plasma levels of CGRP are increased in soft tissue injuries and in patients with chronic cardiac failure and sepsis, indicating that CGRP may be another important peptide in chronic illness. Animal experiments have shown that rats depleted with sensory neuropeptides show reduced inflammatory responses, as well as poor wound healing and diminished skin integrity.

CGRP seems to be of importance in the formation of new vessels through the induction of endothelial cell proliferation during pathophysiological events such as ischemia, inflammation, and wound healing. In the survival of ischemic denervated tissue, the importance of reinnervation of mainly CGRP-containing fibers has been stressed. These data suggest that the healing process is also related to the anti-inflammatory effects of CGRP, and upregulation of CGRP binding sites are reported in selective brain areas (involved in the integration of sensory information) following stress.

**Immune system**

Neuropeptides are capable of interacting with almost all components of the immune system. CGRP is a potent anti-inflammatory mediator; it is thought to inhibit type 1 cytokines (eg, interleukin [IL]-12 and interferon γ) and to enhance the production of IL-10, one of the most immunosuppressive cytokines. Gomes et al observed anti-inflammatory effects of CGRP in models of acute peritonitis, reducing the recruitment of neutrophils induced by treatment with lipopolysaccharides. The anti-inflammatory effect of CGRP is comparable with the proinflammatory effects of SP, bradykinin, and endothelin and suggests that different vasoactive peptides could participate in opposite ways on macrophage activation during local and systemic acute inflammation and possibly bacterial sepsis.

**CGRP AND BURNS**

The reaction after a local burn injury is dependent on the temperature and duration of the burn. Several experimental investigations have shown that the delayed phase in burn inflammation is mediated by humoral and neurochemical factors, and pharmacological
intervention could therefore be of clinical importance. The contribution of sensory neuropeptides has been shown in the delayed phase. Several vasoactive neuropeptides have been proposed as mediators of the delayed phase reaction.

Although not necessarily connected, the similarities between neurogenic inflammation and the reactions after a burn injury are intriguing. The role of neurons in the response after a burn injury was first suggested by Sevitt, who observed that denervated skin showed a higher (2–3°C) threshold temperature at which plasma extravasation developed. By applying a hot iron to the skin, he showed that a specific temperature initially induced an erythema and if the application was prolonged, plasma extravasation could also be observed. With decreasing temperatures, proportionally longer heat exposure was required for the development of edema. In this context, it is interesting to note that the threshold temperature for edema formation has been estimated to 45°C, and that this is similar to threshold temperature for the activation of nociceptive fibers in the skin. Furthermore, in more severe burns, edema can also be observed in subdermal structures and this has been correlated to subdermal temperatures of 41°C to 45°C during the time of exposure. Early and delayed edema formation has been demonstrated in burns of different severity. In more severe burns, the early part is rapid in onset and the delayed part is often indistinguishable from the early or abolished part due to stasis produced by the early massive edema formation. In milder burns, the early part is less pronounced and sometimes followed by a distinct delayed increase in edema formation occurring 4 to 8 hours postburn. This latter effect can be observed after a well-defined exposure of the skin to hot water (60°C, 10 seconds).

The first evidence for the importance of nociceptive C-fibers was obtained in 1983. It has been shown that capsaicin pretreatment reduced edema formation after a mild (48°C, 5 minutes) scalding injury, and that this edema was also reduced by an SP antagonist but not by antihistamines.

Burn injury leads to the release of SP and CGRP from nociceptive sensory endings. CGRP and SP contribute to the spread of edema by acting directly on venules to produce vasodilatation. CGRP affects the regulation of local blood flow, smooth muscle tone, and glandular secretion. Siney and Brain confirmed these findings in rat dorsal skin by the use of selective SP and CGRP antagonists. SP and CGRP also seem to play a role in the initial plasma extravasation observed after thermal injury in rat dorsal skin.

SP has a major role in the initial plasma extravasation after injury. Moreover, CGRP is involved in mediating plasma extravasation for up to 15 minutes after the onset of thermal injury. Löfgren et al demonstrated increased concentrations of CGRP-LI in a perfused rat paw following thermal injury, and thermal injury resulted in a unilateral increase in blood flow paralleled by an increased content of CGRP-LI and NKA-like immunoreactivity in paw perfusate. The thermally induced inflammation of the rat paw caused locally increased perfusion, which was characterized by 2 phases. Notably, the second phase was significantly reduced by pretreatment with NK1, NK2, or CGRP receptor antagonists, suggesting that the secondary phase is neurogenically mediated.

The neuroendocrine system through the release of CGRP and SP may play a role in the pathogenesis of sepsis. High systemic CGRP levels were associated with lethal outcome already at the onset of sepsis, whereas high SP levels were identified as late predictive indicators of lethal outcome.
Onuoha and Alpar\textsuperscript{38} examined the concentration of sensory peptides in human thermal injuries, on admission and 24 hours postadmission, and their role in the metabolic, immunological, and inflammatory complications. Basal levels of CGRP and SP were significantly higher in patients with burn injuries than in the healthy control subjects.\textsuperscript{38} These results support the concept that the neuroendocrine system through the release of CGRP may play a critical role in the pathogenesis of sepsis.\textsuperscript{12,38,104}

CONCLUSIONS AND FUTURE PERSPECTIVES

This review has summarized, and attempted to correlate, the inflammatory activities of CGRP in burns. There have been previous reviews on the cardiovascular activities of CGRP\textsuperscript{71,80,81} that relate to this fascinating peptide family.\textsuperscript{76,78} Its most important activity is its potency in peripheral vasodilation.\textsuperscript{44,125–127} Several studies have shown that sensory peptides are released from peripheral nerve endings during a noxious or thermal stimulus, such as a scald, and may thus contribute to the pathophysiology of burn injuries.\textsuperscript{12,38,103,119–124} This suggests that, as described in this review, it probably plays an important role in the regulation of tissue perfusion, inflammation, and healing and tissue repair.\textsuperscript{12,38,103,119–124} More information regarding the concentration of CGRP in plasma in human burns is needed. It will be interesting to follow plasma concentration of CGRP in patients with burn injuries, from injury to healing, analyzing the burn for extension, location, and complication (sepsis, organ failure).

This may explain the impact of neurogenic inflammation in burn shock, and perhaps CGRP levels can be used as a prognostic factor in the clinical setting. In this way, it may be possible in the future to modulate the systemic response to burn to improve burn care. In recent years, the synthesis of nonpeptides that are capable of antagonizing effects mediated via the CGRP receptors has been a major advance.

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