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Evidence for physiological and pathological roles for sensory nerves in the microvasculature and skin

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ABSTRACT

This review highlights the progress from the initial finding of neurogenic inflammation up to the most recent development in the field of sensory nerves research, focusing on their roles in the microvasculature and the skin. Recent discovery of Transient Receptor Potential (TRP) channels highlight their important roles in detecting a range of environmental stimuli, including chemical and temperature. This provides us novel mechanisms for driving neurogenic inflammation upstream of neuropeptide release in addition to promising potential therapeutic targets in various diseases, including pain, itching and skin inflammation.

1. Introduction

1.1. History

Neurogenic inflammation is a mechanism by which sensory nerves contribute to the inflammatory process. The sensory nerves involved mainly comprise of slowly conducting, unmyelinated C-fibres and thinly-myelinated Aδ-fibres. There is a rich history of sensory nerve research. An early study on how sensory nerves may contribute to inflammation was initiated by Stricker in 1876 [1]. He observed that dorsal roots when stimulated caused an increased blood flow in the skin of the area that was innervated by the sensory nerves. This finding was supported by Bayliss in 1901 and Langley in 1923 [2,3]. It was these studies that led to the definitions of antidromic vasodilation, as the dorsal roots only have afferent fibres and removal of dorsal roots abolished the vasodilation (also known as neurogenic vasodilation).

The next important discovery was that the topical application of mustard oil, an irritant chemical, to skin increases blood flow and inflammatory swelling. Similar to the earlier findings, this was also shown to require an intact sensory nerve supply [4]. Sir Thomas Lewis played an important part in allowing the mechanisms of neurogenic inflammation to be further elucidated through his studies into responses to skin injury. He is perhaps best known for his description of this injury as a 'triple response'. The three components of this response are a wheal, a flare and a local reddening response. This triple response is similar to that observed when histamine is injected into skin. The wheal response is caused by oedema formation as a result from increased microvascular permeability. The local reddening and the flare are both consequences of increase blood flow. The flare is of particular interest as it arises from an initial stimulus, leading to an area of erythema that spreads further from the site of injection shown to be dependent on an intact nerve supply. The phrase 'axon reflex' was coined where an initial stimulus is able to activate nerves leading to a spread of activation and, in this case, leading to skin vasodilation over quite a large area.

However, despite the early relevance and interest in neurogenic inflammation, studies on this subject were stunted. Only in the 1960s was there a re-emergence building on earlier findings using mustard oil. Jancso et al. [5,6] undertook mechanistic studies to elucidate the mediators which may be involved in this response,

Abbreviations: ATP, adenosine triphosphate; CFA, Complete Freund's Adjuvant; CGRP, calcitonin gene related peptide; CLR, calcitonin receptor-like receptor; CQ, chloroquine; DRG, dorsal root ganglion; GRPR, gastrin releasing peptide receptor; IL, interleukins; IMQ, imiquimod; KO, knockout; Mrgpr, Mas-related G protein coupled receptor; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); NGF, nerve growth factor; NK1, neurokinin 1; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; PAR, protease activated receptor; PGE2, prostaglandin E2; RAMP, receptor activity modifying protein; RCP, receptor component protein; ROS, reactive oxygen species; SP, substance P; TNF-α, tumour necrosis factor alpha; TRP, transient receptor potential; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; TSLP, thymic stromal lymphopoietin; WT, wildtype; 4-ONE, 4-oxo-2-nonenal.

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and soon realised that neurogenic inflammation was not inhibited by classic autonomic antagonists. With this, Jancso et al. also highlighted the importance of another compound, capsaicin, an irritant found in chilli pepper extract, in studying sensory nerves. Capsaicin was shown to have dual roles, where: 1) at low concentration, dose-dependently causes neurogenic inflammation, yet: 2) at repeated, higher concentration leads to sensory nerve desensitisation and loss of neurogenic inflammation response [6]. Soon, Jancso defined a range of chemicals which had the ability to activate sensory nerves. Perhaps, most importantly, Jancso was the first to show the selectivity of capsaicin for sensory nerves and the pivotal finding that capsaicin desensitisation was able to reduce pain sensitivity. His work contributed to important early basic understanding of the links between sensory nerves and skin. Until now capsaicin or related compounds mediated sensory denervation is one of the most common methods to induce sensory depletion or desensitisation. However, despite close links between sensory nerves and the skin, this depletion technique seemed to be specific for targeting small-fibre sensory nerves [7]. These findings were key in realising that transient receptor potential channels (TRP) channels are localised on sensory nerves.

1.2. Sensory nerves and neuropeptides

The sensory nerves, when stimulated, release biologically active neuropeptides towards the periphery and transmit sensory information towards the central nervous system. The main neuropeptides that mediate vascular effects are the tachykinins (substance P/SP and neurokinin A) and calcitonin gene-related peptide (CGRP) [8]. Both neuropeptides act via their subsequent G-protein coupled receptors, with SP acting primarily via the Neurokinin (NK_1) receptor and CGRP via the CGRP receptor complex [9,10]. Interestingly, the CGRP receptor (CLR) also requires co-localisation with a single transmembrane component known as Receptor Activity Modifying Protein 1 (RAMP1), and an intracellular signalling component Receptor Component Protein (RCP) [10]. The neuropeptides can be released together when antidromic impulses reach the nerve ending. This effect is most commonly studied on cutaneous regions as the skin is densely integrated with sensory nerves and C-fibres including those innervating the epidermal layers as free nerve terminals. These nerves are activated by thermal, mechanical and chemical stimuli to play important roles in detecting external environmental changes [11], while driving neurogenic inflammation response in the periphery (Fig. 1). Immediate effects, such as oedema formation and increased blood flow, are thought to be important in potential skin damage or exposure to harmful substances. They allow various inflammatory mediators, and later, inflammatory cells, to enter the exposed site and mediate healing and protection. Attempts to elucidate the neurogenic mediators involved in such response proved to be difficult and contradictory. However, SP is the best-known mediator to increase microvascular permeability and potentially vasodilation [12], while CGRP is a potent microvascular vasodilator and is most probably responsible for the majority of neurogenic vasodilation observed in human skin [8]. Whilst there is considerable information to suggest that neuropeptides are involved in the pathophysiology of skin diseases, there is a lack of understanding of how these neuropeptides are released, and will be further discussed in later section of this review.

The development of non-peptide antagonists for NK_1 receptors has allowed the contribution of SP in inflammation to be evaluated. Clinical trials that have focused on the skin have been disappointing with little beneficial effect in a range of conditions observed. However, small-scale studies have shown various SP antagonists to be beneficial in contact urticaria [13]. Recently, there has been a re-emergence of clinical trials for SP targeting itch (for details, see Neuropeptides in Skin Inflammation). CGRP antibodies and antagonists have also been developed and are currently in clinical trials for migraine. Whilst benefiting migraine, there have been no effects observed on skin or the cardiovascular system as yet. This again questions their roles both physiologically and pathologically. However, it is noted that they have not been extensively investigated in patients with either cardiovascular or skin conditions to date.

1.3. Transient receptor potential channels

While active research on neuropeptides in a range of inflammatory conditions was evident, especially during the 1980s when the physiological roles for neuropeptides were being elucidated, this has subsided in the recent years. This is possibly due to limited understanding of the receptors which were able to detect these stimuli and the subsequent pathways leading to neuropeptide release, and whether these neuropeptides were released neuronally or non-neuronally. Soon, studies using capsaicin led to its discovery as a selective agonist for transient receptor potential vanilloid 1 (TRPV1) with a number of TRP

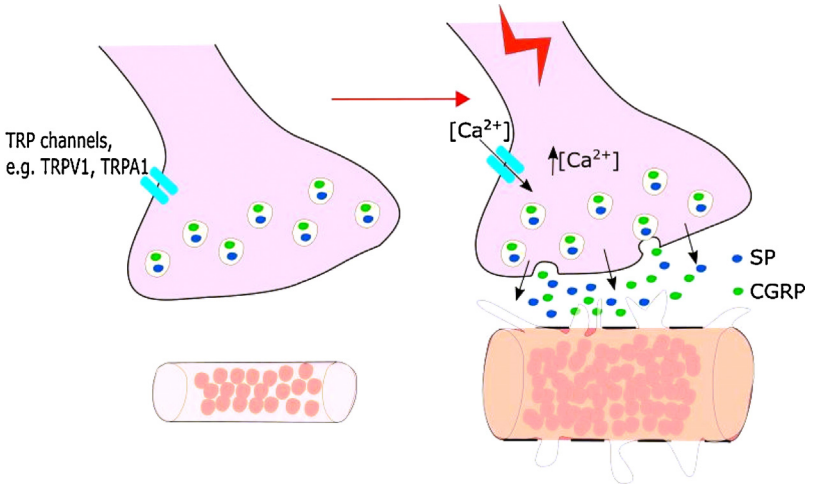

Fig. 1. A diagram representing neurogenic inflammation in the periphery. The stimulation of small-diameter C-fibre terminals resulted in the opening of calcium-permeable ion channels, such as Transient Receptor Potential Vanilloid 1 (TRPV1) or TRP Ankyrin 1 (TRPA1). This results in the release of neuropeptides-containing vesicles towards the peripheral blood vessels, driving vasodilation and increased plasma extravasation. SP: substance P; CGRP: calcitonin gene-related peptide.

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