Complexity of systems and actions underlying neurogenic inflammation

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All components of the body from skin to soft tissue to all visceral organs and bone receive extensive innervation arising from the dorsal roots. Dating to the expression of the “Law of Bell and Magendie”, this innervation is considered to represent the pathway by which afferent or sensory input to the cord occurs. As reviewed in great detail by Valente and Brain [1] in this issue, work in the early twentieth century confounded this notion, with Stricker [2] and later Bayliss [3] demonstrating that information traveling antidromically in the dorsal root could have significant augmenting effects upon peripheral blood flow in a manner independent of the innervation provided by the sympathetic nerves (leading typically to reduced flow), suggesting a “motor” function of this pathway. The role of the sensory afferents was further suggested by the absence of vasodilation after cutaneous denervation [4]. Sensory innervation may vary in its precise composition, but invariably it possesses axons which are myelinated and unmyelinated. A telling association was made by Hinsey and Gasser [5], who showed that cutaneous vasodilation evoked by antidromic stimulation of sensory nerves occurred only if the stimulus was of sufficient intensity to evoke a slowly conducting C fiber potential wave. Following a long and winding pathway, which included the isolation of the peptide substance P (SP) from the dorsal roots and its identification as a vasodilator [6] with a role in plasma extravasation elicited by antidromic stimulation secondary to release of such a neuromediator from chemosensitive small-diameter afferent fibers [7]. Pretreatment of adult rats with the pungent capsaicin resulted in local vasodilation, acute pain behavior, and persistent morphological changes

[8] with an associated functional impairment of chemosensitive C fibers [9]. These observations merged with the classic appreciation that a neuron releasing products at one terminal will release those products at all of its terminals, a variant professed by Eccles [10] of the original expression of the classic Dales law [11]. So, here we are today. These observations and the contents of this issue inspire several thoughts by the editors and we encourage the reader to consider their implications for their own favored system.

The mirror images of the primary afferent terminals

In our current understanding of the neuron in general, and the afferent axon in particular, we can extend Dale’s principle to note that the pharmacology of the central terminal is mirrored by the pharmacology of the peripheral terminal. Thus, the prohormones and synthetic enzymes for the various transmitters synthesized in the dorsal root ganglia (DRG) cell body are transported bidirectionally so that peptides (such as SP) are found in and released from the central (spinal) terminal and are similarly present in and released at the periphery in a SNARE-dependent fashion. [12] Receptors regulating terminal excitability such as reduction by opiates and enhancement by TRPV1 ligand (both endogenous and exogenous) are found expressed in both central and peripheral terminals. [13, 14] Accordingly, in the face of peripheral injury and inflammation, proinflammatory products released in the injury environment lead to afferent terminal activation and sensitization, leading to the release of neurotransmitters at either end. Hence it can be truly said that capsaicin, for example, is the drug that burns at both ends.

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The origins of the axon reflex

While the classic notion is that the peripheral terminal release represents excitation arising from the local axon collateral, the review by Sorkin and colleagues [15] emphasizes that classical physiology has long pointed to the generation of

antidromic activity from different parts of the afferent structure including: mid-axon (as after nerve compression or focal injury), the dorsal root ganglia and the central (spinal) terminal. Further, much work is being undertaken today emphasizing that as the DRG lies outside the blood–brain barrier, its excitability can be regulated by circulating products and inflammatory cells such as macrophages. Through such factors, DRG excitability can be enhanced. Such excitation of the cell body can then lead to both orthodromic and antidromic afferent activity. Work remains to be done to define how these effects on DRG excitability influence the antidromic function. The classic work relating to the dorsal root reflex (DRR) of Barron and Mathews [16, 17] clearly point to antidromic activity arising from the central terminal in the uninjured, normally functioning afferent secondary to focal depolarization in the dorsal horn after an afferent barrage. Finally, of additional interest is the fact that, as reviewed by Sorkin et al. in this issue [15], such DRRs can be initiated by *bulbosacral* projections. [18] Such linkages point to mechanisms whereby supraspinal systems can regulate peripheral afferent terminal excitability.

DRG targets of the antidromic potential

The targets of the axon collaterals have classically been envisioned to be adjacent tissues, e.g. skin and muscle. Such linkages are reviewed in the articles by Choi and DiNardo [19], Birder and Kullman [20] and Feuilloley [21]. An interesting variant on this theme is that afferent axon collaterals also project into the DRG. As reviewed in the Sorkin article [15], peptidergic collaterals are observed in the DRG. These afferent axon collaterals thus deliver terminal neurotransmitters to cells within the dorsal root ganglion. Satellite cells and DRG neurons express a variety of excitatory receptors [23] that may thus lead such axon collaterals to alter local DRG excitability. As noted above, in the face of peripheral injury and inflammation, secretors of active factors such as macrophages appear in the DRG. [22] Neuropeptides and other transmitters released by the local DRG collaterals can thus activate macrophages (as they do in the peripheral terminal), leading to the release of local macrophage products. This mechanism is yet to be fully characterized.

Multiple effects of peripherally secreted afferent transmitters

A theme represented by the contents of this series of invited papers is the multiple effects that can be induced by the antidromic release from the small afferent terminal. Broadly, these effects can be considered in terms of contributions to local neurocircuitry (as the visceral mucosa and to local trophic regulation). Littlejohn [24] points to the potential

contributions to the fibromyalgic pain state presenting an interesting hypothesis of mechanism contributing to this anomalous pain condition. Birder and Kullman [20] point to the role of antidromic activity in regulating the complex local neural circuitry in the viscera in general and the bladder in particular. The importance of neurological connections with other cells is cited in particular by Birder and Kullman, since the neurological connection with mast cells is key in the pathogenesis of cystitis. Mast cells are commonly found in close approximation to SP-positive fibers; therefore, factors released by mast cells upon degranulation stimulate small (typically high threshold) afferent nerves. To support these findings, they examined the urine of rodents with virus-induced cystitis and patients with cystitis, and found high levels of histamine, methylhistamine and tryptase as compared to controls. After mast cell release, tryptase can activate protease-activated receptors (PARs) in the urothelium, in particular PAR1, resulting in inflammation and submucosal neuronal activation. Also very important for these findings are the connection between neuron-secreted neurokinins and the microbiota presented by Feuilloley [21]. He presents studies that demonstrate that the microbiota products, especially gram-negatives binding to TLR4, play an important role in pain after bladder infection; the ligands will directly act on urothelial cells and afferent TRPV1 nerves. But even more important for the future studies on itch and atopic dermatitis is the demonstration that SP secreted by neurons is able to activate transcription factors in *Staphylococcus aureus* and *Streptococcus epidermidis* with the peculiar consequence of turning a friendly microbiome into a more aggressive biofilm-forming bacteria. Feuilloley also discusses the effects of antidromic afferent activity on changes in the local cutaneous microbiome. The breadth of the contributions of the afferent linkages to the microbiome story is further emphasized by recent work showing that antidromic activity can suppress the local immune response in lung infections. [25]

Another area of note is the role played by antidromic afferent activity in wound healing. As reviewed elsewhere [26], products released from the sensory afferent, including peptides such as SP calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP) and neuropeptide Y (NPY), can act upon eponymous receptors expressed on keratinocytes, endothelial cells and fibroblasts. Such neuropeptides have been variously shown to promote endothelial cell differentiation and proliferation and also proliferation of keratinocytes. Blais and co-workers showed that sensory neurons secrete SP and induce a two times faster wound closure in vitro. This effect is completely blocked by a treatment with a specific antagonist of the SP receptor neurokinin-1 expressed by keratinocytes. [27] Neurokinin A is a bioactive tachykinin released into the skin after injury and activates, through neurokinin-2 receptor NK-2R, cutaneous target cells such as keratinocytes and dermal

endothelial cells, thereby modulating skin inflammation during wound healing. Neuropeptides are important in the different phases of wound healing. Neuropeptides like SP, NKA, PACAP, VIP and CGRP are released during the inflammatory phase, while VIP, SP and NKA are important in the proliferative phase, and NGF, CGRP and SP are important in the later remodeling phase as they induce fibroblast differentiation and nerve regeneration. The absence of these essential mediators in denervated skin has been shown to result in delayed wound contraction and a reduced microvascular proliferation [28].

The importance of neuromodulators in skin inflammation has been detailed by Choi and Di Nardo. [19] Many diseases in the skin have a strong neurological component. For example, it has been known for some time that in patients exhibiting post-poliomyelitis residual paralysis, psoriasis spares the limbs that are affected by the paralysis [29], remarkably indicating the neurological component in maintaining the psoriasis in the skin. Another example of skin and a neurological component is pruritus. In the Choi and Di Nardo article [19], we find a detailed consideration of the pathogenesis of itch. In atopic dermatitis, an interesting linkage exists between the neurons of Th2 cells and keratinocytes cells, with Th2 producing IL31 and SP, which stimulates NHC and mast cells to release several products, including histamine. Again, considering the convergence of mechanisms, we can compare the contributions of the antidromic afferent pathway in regulating skin function, as just described with events transpiring in the urothelium [20] and in the meninges related to the mechanisms underlying migraine. Here, local afferent terminal release similarly impacts upon local cells (such as mast cells) which can robustly impact upon the local chemical milieu. Such changes in turn alter the excitability of other local systems, including the local meningeal vasculature and the afferents. These products, as reviewed by Ramachandran, lead to plasma extravasation, sensitization and ongoing activity in the trigeminovascular afferents [30]. All of these events, reflecting upon the common mechanistic motif, are collectively referred to as peripheral “neuroinflammation”.

In short, the above brief comments emphasize the complexity of role played by the afferent axon net that projects to all organ systems throughout the body. It serves not only its eponymous purpose (the afferent pathway), but a complex role in directly modifying the function of the many peripheral systems which they innervate, a truly bivalent system. Finally, the editors wish to extend a sincere thanks to the contributors to this series for their diligence.

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