ISSN: 2641-1911
DOI: 10.33552/ANN.2023.15.000859
Archives in Neurology & Neuroscience
Iris Publishers

Review Article

Peptide Upregulation and Inflammatory Cascading: The Unseen Outcome of Autonomic Dysregulation

Peter Behel*

Department of Psychology, Sonoma State University, USA

***Corresponding author:** Peter Behel is an adjunct Professor at Sonoma State University, and a former President of the Biofeedback Society of California. His work has been showcased in the former New York Times No. # 1 Bestseller, 8 Weeks to Optimum Health, USA, **Email:** behel@sonoma.edu.

Received Date: April 13, 2023

Published Date: May 08, 2023

Abstract

Peptide upregulation is an essential component of the pain signal transmission process known as nociception. During nociception the body's principle excitatory neurotransmitter glutamate is co-released with the neuropeptide substance P to relay pain signals from the periphery to the central nervous system. Various studies have determined that the autonomic nervous system exerts a stimulating effect on substance P, and the extent to which substance P plays a primary role in pain signal conduction underscores the influence that autonomic functioning has on nociception itself. Insofar as the release of substance P is responsible for producing an extended inflammatory profile, hyperactive sympathetic nervous system functioning represents a largely unaccounted for mechanism involved in perpetuating inflammatory cascading.

Introduction

Substance P is a member of the tachykinin neuropeptide family widely known for its involvement in pain signal transmission and pain mediation. Studies have indicated that substance P plays a significant role in anxiety and depression [1], yet what is especially noteworthy is the cascading effect that the release of substance P initiates, which produces what is popularly referred to as inflammatory soup. This chain response encompasses multiple inflammatory mediators whose collective interaction includes the release of cytokines and chemokines. To the extent that various health disorders involve the extended presence of inflammatory mediators, reviewing the role that autonomic dysregulation plays in perpetuating inflammatory cycling would seem to be a process worthy of additional inspection.

Stress / Immune Interaction

Inasmuch as substance P [SP] contains proinflammatory properties [2], it is worth noticing that it is also released by immune cells in addition to the peripheral nerves. This sets up a bidirectional interaction involving stress and immune system functioning whereby inflammatory regulation can be influenced by stress and emotions [3]. By extension, substance P dysregulation is associated with the pathophysiology of anxiety and depression, in addition to the pathophysiology of inflammatory disease [4]. Substance P's biological activity is mediated through neurokinin receptors [NKRs], particularly NK1R [5]. In accordance with its role as inflammatory mediator, substance P moderates the interaction between nociceptive neurons and immune system functioning [6].

In the periphery SP is typically released as a result of nociceptor activation following tissue damage [7]. Intriguingly however, tissue injury is not necessarily required to release the neuropeptides and neurotransmitters that are involved in the nociceptive response, an occurrence that is occasionally referred to as psychogenic [8]. Additionally characterized as maladaptive or pathological, impending tissue damage by itself constitutes sufficient criteria

to trigger nociceptive neurotransmission, without actual tissue damage being required [9]. To this end, it has been postulated that nociceptors enter into a persistent hyperfunctional state where central neural, glial and inflammatory signal combinations interact to produce spontaneous action potential generation in the periphery and hyperexcitable nociceptors within the dorsal root ganglia of the spinal cord [10]. This nociceptive priming over time reduces the level of inflammatory mediator concentrations necessary to stimulate elevated pain responsiveness [11].

Neurogenic Inflammation

Various neural models suggest that the nervous system is organized to anticipate potential pain and adjust its output before the risk of tissue damage becomes critical [12]. Neurogenic inflammation consists of complex interactions among inflammatory mediators that incorporates somatosensory, immune, autonomic and vascular systems. The outcome of these interactions leads to nociceptor hyperexcitability, which then increases the production and release of inflammatory neurotransmitters that induce pain [13]. While peripheral nervous and immune systems have traditionally been regarded as serving individual functions, it is now recognized that the coordinated interaction of peripheral neurons with immune cells form an integrated protective network that encompasses the presence of inflammatory mediators [14]. Because of the bidirectional nature of this interaction, neuropeptide release initiates a systemic stress response through sympathetic nervous system activation, and the same neuropeptides mediate both stress and inflammation [15].

Mast Cell Activation

Mast cells are tissue-residing immune cells responsible for initiating allergic reactions. They are located in close proximity to peripheral nerve endings and serve as an essential link between nervous system and immune functioning. Mast cells stimulate allergic symptoms by releasing mediators that are stored in granules within the mast cells. They are involved in the recruitment of various immune cells, and mast cell /neuron crosstalk is associated with pathologies ranging from arthritis to post-surgical pain [16]. While known for their function in allergic reactions, mast cells have gained recognition for their role in inflammatory conditions such as psoriasis and multiple sclerosis. Mast cells can be activated by non-allergic triggers such as neuropeptides and cytokines, and they also selectively release pro-inflammatory mediators [17]. This can initiate a cycling dynamic where the release of nociceptive inflammatory mediators such as SP and calcitonin gene-related peptide [CGRP] induce the release of histamine from adjacent mast cells, and histamine in turn provokes the release of substance P and CGRP [18].

As circumstances might have it, the neural release of substance P and the binding of SP to its NK1 receptor [NK1R] on the mast cell surface is, in fact, one of the mechanisms that activates mast cells [19]. Subsequently, the cycling dysregulation of SP release results in mast cell activation and mast cell degranulation [20]. Disordered mast cell activation is said to take place when mast cells are pathologically overproduced, or if their activation is out of proportion to the perceived threat of homeostasis [21]. Following activation, mast cells exude granule-associated mediators and generate lipid-derived substances that induce allergic inflammation [22]. Mast cell degranulation releases an assortment of mediators in response to the activating signals, including histamines [23], prostaglandins, bradykinin and leukotrienes [24]. This degranulation is associated with the activation of the neurogenic inflammatory response that is reported to potentiate following traumatic brain injury [25].

Prostaglandins are a group of regulatory compounds that are produced at the site of tissue damage or infection that facilitate repairs. They maintain homeostatic functioning and also mitigate pathogenic mechanisms such as inflammation, blood flow and blood clot formation [26]. While prostaglandins have long been recognized as mediators of acute inflammation, recent studies have indicated that they additionally contribute to chronic inflammation through the amplification of cytokine signaling and chemokine recruitment [27]. What is noteworthy here is that sympathetic postganglionic neurons are responsible for producing prostaglandins, and the release of prostaglandins is said to contribute to sympathetically maintained pain [28]. This represents an additional layer that elevated sympathetic nervous system activation provides, insofar as triggering inflammatory cascading is concerned.

Along with leukotrienes, prostaglandins make up one of the two major pathways of what is referred to as eicosanoid metabolism [29]. Eicosanoids, including pro-inflammatory prostaglandins and leukotrienes, are biologically active lipids that are involved in multiple pathological processes ranging from inflammation to cancer. The molecular mechanisms underlying the interactions of eicosanoids, leukotrienes and prostaglandins are key mediators in the orchestration of cancer progression, tumor evolution and metastasis [30].

Nociceptor Priming/ Inflammatory Cycling

A significant feature of these inflammatory interactions involves the cycling nature of their release. For example, prostaglandin signaling elicits histamine release, potentiates acute inflammation and triggers mast cell activation [31]. When mast cells are activated, eicosanoids and leukotrienes are released [32]. Mast cell activation is also followed by cytokine and chemokine secretion, both of which contribute to chronic inflammation [33].

The assortment of inflammatory mediators said to be induced by stress and danger-associated molecular patterns includes adenosine triphosphate (ATP), a purine whose release also leads to the activation of mast cells and macrophages [34]. Serotonin (5HT) is another component of the so-called “inflammatory soup”, whose release increases action potential firing and sensitizes nociceptive neurons during inflammation [35].

The extent to which inflammatory mediator release stimulates nociceptor priming, lowers synaptic thresholds and increases nociceptor signaling exposes an interactive relationship where increased nociceptive activation results in elevating the presence of inflammatory mediators, and the extended release of inflammatory

mediators in turn increases nociceptive signaling [36]. This increased nociceptor output is subsequently responsible for inducing the hyperalgesic priming associated with pain signal elevation referred to as "wind-up" [37].

Substance P and Stress

Substance P specifically is reported to exert proinflammatory effects through mast cell activation, along with corticotropin-releasing hormone (CRH) as a result of stress [38]. This is evident in conditions such as interstitial cystitis, irritable bowel [39], and fibromyalgia [40]. Not only is substance P mediated mast cell activation involved in intraplaque hemorrhage and vascular inflammation in atherosclerosis [41], but mast cell degranulation plays an active role in the pathogenesis of conditions as diverse as asthma, vasomotor rhinitis and pulmonary fibrosis [42], as well as cardiovascular diseases [43]. As it turns out, the etiologies and symptoms associated with mast cell dysfunction have gained sufficient recognition that the term mast cell activation syndrome (MCAS) is now regularly used to refer to the generation of pathologies that also includes multiple sclerosis (MS), ulcerative colitis and Crohn's disease [44].

Moreover, neurogenic inflammation itself is predicated on the release of the inflammatory neuropeptides substance P and CGRP [45]. Substance P provokes the release of inflammatory compounds such as interleukins, growth factors and chemokines, and activates mast cells to release inflammatory mediators such as cytokines, arachidonic acid, histamine, prostaglandins, leukotrienes and various other assorted inflammatory mediators whose collective interaction constitutes what is colloquially referred to as inflammatory soup [46]. Subsequently, it has not only been asserted that elevated levels of substance P are present in all chronic and acute inflammatory conditions, but that it is possible to interfere with the process of inflammation by blocking SP release or SP receptors [47]. By extension, blocking SP might possibly prove to be a worthwhile avenue of treatment insofar as alcohol use disorder is concerned [48].

Generalized references to the effects of stress are often dominated by abnormal hypothalmic-pituitary-adrenal (HPA) axis output associated with the downstream production of cortisol. Scant attention is placed on neuronal-based stress mechanisms whose response patterns become enmeshed within the functioning of the circuitry itself. The contributions of neurotransmitters to mast cell activation and inflammatory cascading highlight a multifaceted cross-talk dynamic where mast cells are modulated by neuropeptide release, as a result of bidirectional stress/ immune system interactions. Accounting for the downstream impact that inflammatory cascading produces effectively redefines the scope of what a stress response consists of.

Autonomic Dysreflexia

Conducting synaptic traffic from the periphery to the central nervous system represents an integral aspect of nervous system functioning that is not always associated with autonomic dysregulation. Yet dysautonomia appears to be a factor when it comes to pain signal processing, an operation reliant on autonomic functioning. While nociception normally generates relatively mild levels of attention, the ensuing release of inflammatory mediators can perpetuate without resolution, a seemingly rogue response not always recognized as the outcome of stress-related triggering. The extended value added recognition carries lies within the prospect of excessive sympathetic stimulation becoming down-regulated through targeted autonomic regulation, a process that can be employed to modify and decrease the presence of cycling inflammatory mediators with no resulting possibility of hazardous or toxic side effects.

This opens up opportunities for ameliorating dysregulated autonomic functioning at its point of inception that otherwise remain unavailable. Targeting nociceptive transmission at the first synapse in the spinal dorsal horn has been promoted as an efficacious pain treatment approach that's free from the unwanted side effects associated with the engagement of opioid receptors in the brain [49]. Even though modifying nociceptive traffic has been readily utilized with moderating inflammatory mediators in mind [50], impairment in generating reflexive measures aimed at resolving inflammation has been theorized as leading to chronic disease, and disease pathophysiology [51]. Perhaps that's why recent findings show that the hyper-inflammation generated by COVID-19 corresponds with mast cell activation symptoms and severity reported by Long COVID sufferers [52].

Acknowledgement

None.

Conflict of Interest

No Conflict of interest.

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