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Neuromediator and its Receptor in Mast Cells Biology

Dr. Md Abdul Alim, PhD [1,2]*

1. Uppsala University, Department of Medical Biochemistry and Microbiology, Uppsala, Sweden.

2. Department of Public Health and Caring Sciences, General Medicine and Preventive, Medicine, Uppsala University, Uppsala, Sweden.

Corresponding Author: Dr. Md Abdul Alim, PhD, Department of Medical Biochemistry and Microbiology / Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden.

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Abstract

Whether neuromediator displays a pathway of signaling to mast cells has been mysterious until recently when the expression of glutamate receptors on mast cells was established by both in-vivo and in-vitro studies. We recently demonstrated that exposure of mouse mast cells to neuromediator (e.g., glutamate) activates a broad range of glutamate receptors, of both ionotropic and metabotropic types. Our earlier studies also indicate that mouse mast cells may respond to glutamate receptor antagonists. It was further observed that the exposure of mast cells to glutamate resulted in an increased level of pro-inflammatory cytokines/chemokines and transcriptional response, introducing the concept of a glutamate-glutamate receptor axis in mast cells, which can contribute to neuroinflammation and pain regulation in peripheral soft tissues (e.g., tendon). Different neuromediator including glutamate, Substance P, and calcitonin gene-related peptide (CGRP) have the excitatory response both in the peripheral and central nervous system and have been implicated in various diseases including pain, neurogenic inflammation, and cancer. Optimal neuromediators response is crucial for the body but in excess, however, it is harmful and causes many disorders including neuronal death through a massive calcium influx via its specific (e.g., glutamate via ionotropic and/or metabotropic) receptors. The glutamate-glutamate receptor axis in mast cells is exclusive. However, mast cells are emerging players in the communication between peripheral nerve endings and the immune system. It is not so clear by what mechanism mast cells interact with nerves/tenocytes and how the functionality of mast cells depends on glutamate binding and stimulation. In this review, we will address the role of different neuromediators-receptors especially glutamate/SP on mast cell function as well as summarize the possible mechanisms of the neuromediator-receptor axis on mast cells/nerves during healing, neurogenic inflammation, and pain responses in the context of in tissue injury.

Keywords: *Neuromediator, glutamate receptors, mast cells degranulation, MK801, nerves, tenocytes.*

Introduction

Neuromediators and their regulation in mast cells have been implicated in many pathophysiological processes, in line with the notion that neural regulation contributes to health and disease and presents a range of potential therapeutic purposes [1]. However, the full extent to which mechanism mast cell-nerve interactions influence health and disease are still a matter of debate, and a complete understanding of the molecular mechanisms underlying the relationship between mast cells and the nervous system is crucial [1, 2].

Nevertheless, it has been reported that mast cells can express different receptors for various neurotransmitters, including glutamate (Glu), acetylcholine (Ach), the gaseous neurotransmitters nitric oxide (NO), gamma-aminobutyric acid (GABA), and dopamine (DA); neuropeptides such as substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), corticotropin-releasing factor (CRF), neurotrophins (NTs) and neurotensin (NT), adenosine triphosphate (ATP), tachykinin, opioid, and other neuromodulators [3-5]. Glutamate (also referred as glutamic acid) is one of the most abundant excitatory neuromediators/neurotransmitters of both the peripheral and central nervous system [6-8] and has been involved in various pathological disorders including Parkinson's disease, anxiety/depression, insomnia, pain and inflammation [3, 9]. It is an extracellular messenger molecule in many tissues, engaged in both neural and non-neural signaling. Glutamate signaling affects central and peripheral tissues (e.g., brain, bone, tendon, joints, etc.) and mediates several disease settings including pain, lung cancer, Parkinson's disease, and rheumatoid arthritis [10-13]. Previously, we demonstrated that a high level of glutamate is released from the peripheral nerve ending and this was accompanied by upregulated expression of the glutamate receptor NMDAR1 in a rat model of tendon injury [3, 14].

In addition, we noted that the tendon injury was escorted by extensive mast cell degranulation, suggesting that the injury may be related to the activation of the tissue-resident mast cell compartment [14]. In the soft tissue healing mechanism, the peripheral nerve system (PNS) displays a key role in regulating inflammation, pain responses, and healing of the damaged tissue via afferent to efferent pathways [15, 16]. It has been reported that peripheral nerve endings at the site of injury can release different powerful neuromodulators including glutamate, Substance P, and CGRP which have a key role in tenocytes (fibroblasts-like cells) activation in the healing and pain-afflicted tendon tissue [12, 14, 15, 17]. Released neuronal substances may also interact with resident mast cells and macrophages to affect their function [14, 18]. Conversely, mast cells contain substances that, when released, may alter the function of both the PNS and tissue cells [3, 15].

Previously, it has been hypothesized that mast cells residing near nerve endings may degranulate and affect the function of the PNS, which makes them a potential target for modulating chronic inflammation and pain. In addition, mast cells can respond to glutamate stimulation by mounting a functional glutamate: glutamate receptor axis, thereby introducing a novel principle for how the immune system can interact with nerve cells and how mast cells function is regulated by neuromediator signaling. In this review, we will address neuromediator signaling in mast cell degranulation and function as well as summarize the possible impact of neuromediator-receptor axes on mast cells during healing, inflammation, and pain responses in the context of tissue injury.

Mast cells and neuro-inflammatory mediators

Mast cells are important immune cells, contributing both to innate and adaptive immune responses. These cells are hematopoietic and granulated cells of the myeloid lineage that are mostly found in connective tissues, skin, and mucosal surfaces. They are also found as resident cells in various parts of the body including different soft tissues (e.g., tendon, muscle- bone joints, or tendon-bone joints), meningeal, membranes of the central nervous system, and the pancreas **[**14, 19-21**]**. The tissue-resident mast cells originated from an early embryonic wave of cells from the yolk sac **[**22**]**. Besides allergic diseases, mast cells also mediate various inflammatory responses, by their capacity to release enormous amounts of multiple proinflammatory mediators. Accordingly, mast cells participate in many physiological and pathophysiological responses related to inflammation, chronic wound healing, and autoimmune diseases **[**15, 23**]**. One of the major aspects of mast cells is their high content of secretory granules, which are mostly filled with numerous types of preformed and/or de-novo inflammatory mediators, including biogenic amines (e.g., histamine, serotonin), different growth factors, cytokines/chemokines, proteoglycans, lysosomal enzymes and various proteases (e.g., tryptase, chymase, and carboxypeptidase A3) **[**3, 15, 24**]**. Mast cells are activated via IgE receptor crosslinking or in response to numerous other triggering systems **[**25**]** and undergo degranulation by resealing secretory compounds to the external environment of the cells. Mast cells have been implicated in both roles as in protective host responses towards external insults **[**26**]** and are also well known for their detrimental impact on inflammatory conditions.

In addition, there is emerging evidence suggesting that mast cells potentially could be involved in conditions associated with peripheral nerve signaling, as characterized by a proposed role for mast cells in mediating pain and tissue healing response **[**3, 26**]**. Previously, we have also been able to demonstrate functional mast cell: nerve interaction as evidenced by mast cells present in close

association with peripheral nerve endings [27, 28]. However, the underlying mechanisms of mast cell-nerve signaling are incomplete. Our previous study supported the most possible mechanisms where mast cells released secretory products and can interact with nerve endings and tenocytes [3, 15]. Furthermore, these secretory products including glutamate, histamine, and serotonin, may interact with corresponding receptors on afferent neurons [29-31]. Additionally, it has been proposed that tryptase (a serine protease) is found in large quantities in the mast cell compartment [32]. The proteolytic activity of tryptase can thereby activate protease-activated receptor 2 (PAR2) expressed by afferent neurons, thereby triggering nerve signaling [33, 34]. We proposed that an autocrine loop can be generated in which nerve endings activated by mast products release neuropeptides (e.g., glutamate, Substance P, CGRP), which can activate mast cells through, e.g., NK1 receptors, thereby amplifying the cascade of mast cells activation/nerve signaling [35].

The Role of Glutamate and its receptors in mast cells

Glutamate is a highly abundant excitatory neuromediator and is essential for many aspects of normal brain function such as learning and memory [36, 37]. In excess, however, glutamate is harmful and causes neuronal death by causing a massive calcium influx via ionotropic glutamate receptor channels, with consequent damage to mitochondria and activation of proapoptotic genes (Fig 1). Glutamate toxicity occurs as part of the ischemic cascade associated with spinal cord injury, stroke, traumatic brain injury, and various diseases of the central nervous system, including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, and multiple sclerosis as well as soft tissue healing and inflammation [36, 38-40]. Its actions are mediated by ionotropic (ion channel–forming) and by metabotropic (G protein–activating) glutamate receptors (Fig. 1).

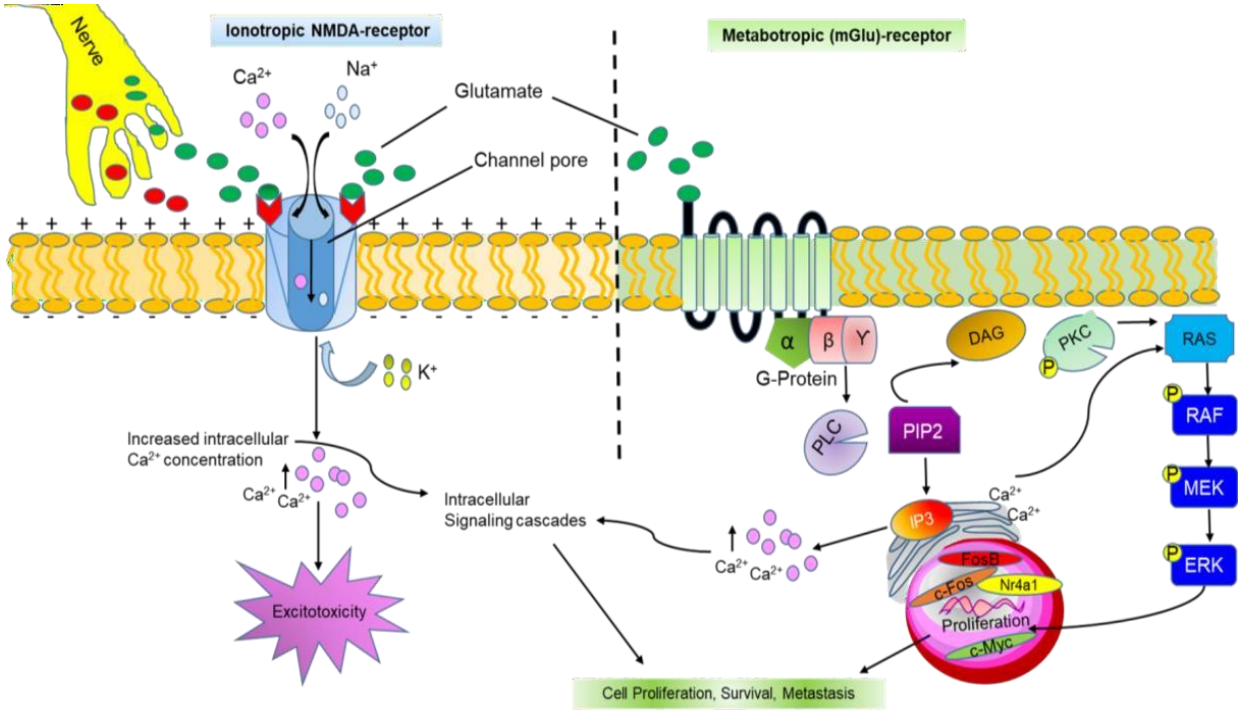

Figure 1. Glutamate signaling pathways and regulation of downstream signaling cascades activation via both ionotropic and metabotropic glutamate receptors. Glutamate (green dot) binds to its binding site on the receptors and increased intracellular calcium concentration and activates downstream signaling cascades including transcriptional and nuclear activation/regulation following cell proliferation, differentiation, ¨survival, and metastasis. Basically, this glutamate signaling starts when this signaling molecule binds to its receptor (ionotropic/metabotropic) on the cell surface and ends when the DNA molecules in the nucleus express a protein and produce some changes in the cell through the cell division. These signaling pathways involved many proteins, including MAPK (mitogen-activated protein kinases, also called ERK, extracellular signal-regulated kinases), which communicate by adding phosphate groups to a neighboring protein, which acts as an "on" or "off" switch. (This figure is edited with Bio Render).

The ionotropic glutamate receptors are mainly coupled with ion channels and are grouped into four distinct classes based on pharmacology and structural homology: the NMDA receptors (e.g., NMDAR1, NMDAR2A-NMDAR2D, NMDAR3A, NMDAR3B) **[**41, 42**]**, the AMPA receptors (e.g., GluA1-GluA4) **[**43**]**, the kainite receptors (e.g., GluK1-5) **[**44**]**, and the δ receptors (GluD1 and GluD2) **[**45**]**. The metabotropic glutamate receptors which may include group I (mGlu1R and mGlu5R; coupled to Gq/G11 proteins), group II (mGlu2 and mGlu3; coupled to Gi/Go proteins), and Group III (mGlu4, mGlu6, mGlu7, and mGlu8 receptors; coupled to Gi/Go proteins) metabotropic receptors **[**15, 46**]**.

Among them, glutamate receptors, NMDAR1, an ionotropic N-Methyl-D-Aspartate (NMDA) receptor, have been in focus in studies of various pain-related conditions, including studies on tendinopathy and tissue inflammation [47]. It is a heteromeric complex protein consisting of four subunits derived from three different protein families (NMDAR1, NMDAR2, and NMDAR3) [48]. However, the composition of these subunits can vary depending on cell type and this can affect their functional properties [49]. In patients with chronic tendon pain, a 10- fold up-regulation of NMDAR1 expression has been observed in transformed tenocytes, in the endothelial and adventitial layers of neovessel walls, and presumed sprouting nerve fibers [50]. The nerve in growth in combination with the expression of different pain signaling molecules may be important in pain regulation both in tendinopathy, and tendon healing as well as in the inflammatory process. Intriguingly, we showed recently that NMDAR1 was strongly upregulated in a rat model of tendon injury, and we noted that the tendon injury was accompanied by extensive mast cell degranulation, suggesting that the injury may be related to activation of the mast cell compartment [14]. Moreover, we demonstrated that NMDAR1 co-localized with mast cells in the injured, but not the healthy, tendon [14]. These findings raise the intriguing possibility that glutamate receptor expression may be induced in mast cells activated by nerve signaling mechanisms and that such mast cell-expressed glutamate receptors have a functional impact on how nerve cells and the peripheral immune system interact.

A more detailed analysis has revealed the specific localization of the different glutamate receptors in painful tendons. NMDAR-1 and phospho-NMDAR1 were detected on sprouting nerve fibers, newly formed blood vessels, and transformed tenocytes [51]. These localizations suggest the involvement of glutamate receptors in tendinopathy regulating the excitability of pain transmission on nerve fibers, the proliferation of endothelial cells, and tenocyte apoptosis. Recent reports on glutamatergic signaling in patients with chronic tendon pain demonstrated that elevated glutamate coexistence with up-regulation of its receptors, NMDA1 and phospho- NMDA, in sprouting nerve fibers of the tendon. In contrast, such a correlation between glutamate levels and corresponding receptors was not seen in healthy controls [50, 51]. One recent finding has established a possible mechanism responsible for activating NMDAR-1 in painful tendons. It was demonstrated that the elevated occurrence of NMDAR-1 was positively correlated to the occurrence of SP in painful tendons, while healthy controls exhibited no correlation [51]. These data suggest that SP may be involved in the upregulation of NMDAR1. In fact, SP is known to activate NMDAR1 by removing the magnesium block and thereby increasing the excitability of NMDAR1 [52].

The role of Substance P, CGRP, and their receptors in mast cells

In our earlier studies, we have discussed that chronic painful tendons show an increased number of sprouting sensory nerve fibers and mast cell accumulation in the injury site [3, 14]. Importantly, these nerve fibers express various neuromediators including SP and CGRP. It has been reported by many studies that SP is a more abundantly expressed sensory neuromediator, released from the peripheral sensory nerve ending during inflammation. In addition, it has also been described that SP has a functional impact on both mast cells degranulation/activation and cytokine production, which might be involved in the pathogenesis of various neuro-inflammatory diseases including asthma, psoriasis, multiple sclerosis, AD, rheumatoid arthritis, atherosclerosis, rhinitis, and others [53-56]. Furthermore, SP-mediated mast cell activation leads to cardiometabolic diseases including abdominal aortic aneurysm, obesity, and diabetes mellitus, [4, 57]. In addition, SP primes toll-like receptor (TLR) 2-mediated activation of human mast cells by upregulating TLR expression and potentiating signaling pathways linked to TLR, suggesting that neuronal responses may contribute to innate host defense responses [62]. It has also been reported that SP provokes the expression of functional corticotropin-releasing hormone receptor-1 (CRHR-1), whereas CRH induces neurokinin-1 (NK-1) gene expression in LAD2 human leukemic mast cells, thus potentiating inflammatory diseases affected by stress [63]. The neural release of SP and SP binding to its receptors on the MC surface is one mechanism of mast cell activation (Fig. 2). Earlier experimental studies have demonstrated that SP can induce mast cell activation in an NK-1 receptor (NK-1R)-dependent fashion [6]. Therefore, current evidence also suggests that SP and NK-1R are viable targets for interventions that specifically address various dermatologic conditions, and a selective NK1 receptor antagonist might be a viable treatment option for psoriatic pruritus individuals [64, 65]. In addition to this observation, another study has reported that SP/NK-1R is essential to cause increased numbers of mature mast cells in the hypertensive heart, but however, NK-1R is not required for the activation of cardiac mast cells in vivo [58]. Nevertheless, increasing evidence suggested that SP activates mast cells primarily through the G protein–coupled, Masrelated gene X2 receptor (MrgprX2) [67, 68].

Thus, it is assumed that SP might signal via MRGPRX2 to activate in-vitro cultured human mast cells, resulting in mast cell degranulation and rapid release of small granular compounds [69], mediated neurogenic inflammation and pain in an incision mouse model [72]. Some other studies have also demonstrated that SP effects on cell proliferation are related to degenerative changes associated with tendinopathy, in addition to pro-inflammatory and pain- triggering mechanisms. SP may, in addition to its role in nociception, initiate a proinflammatory response by regulating vasodilation, plasma extravasation, and release of cytokines and chemokines. Moreover, SP promotes the proliferation of

fibroblasts and endothelial cells, and possibly also transforms fibroblasts into myofibroblasts by increasing the production of transforming growth factor beta (TGF-β). Thus, an abnormal increase in SP level may contribute to tendinosis, i.e., fibrotic changes observed in tendinopathic patients, such as cell transformation, hypercellularity, and hypervascularization. Interestingly, sensory nerve endings seem to also express modulatory mediators with anti-inflammatory actions and supposedly anti-nociceptive effects.

Role of other neuromediators/receptors in tendon and mast cells

Tendons may also exhibit autonomic neuromediators, mostly found in type IV nerve endings. The sympathetic mediator norepinephrine (noradrenaline, NA) together with neuropeptide Y (NPY) are released upon injury or nociceptive involvement, while the parasympathetic mediators acetylcholine (ACh) and vasoactive intestinal polypeptide (VIP) are released by vagus nerve activation, denoted the 'cholinergic anti-inflammatory pathway'. Interestingly, while the ACh (parasympathetic) is upregulated in tendinopathy, while sympathetic noradrenaline has been found downregulated. This disbalance of parasympathetic/sympathetic signaling, with a reduction in Vaso regulatory noradrenaline found in nerves around blood vessels and free nerve endings, would seem to reflect effects related to an altered blood flow and a suppressed anti-nociceptive function **[**59, 60**]**. In support of a nerve-mast cell axis, the SP receptor NK-1 and CGRP receptors CRLR and RAMP1 have been identified on mast cells [60**]**. Interestingly, also an opioid, and opioid-like pathways, such as activation of delta-opioid receptors, cannabinoid receptor 1, and somatostatin receptor cause suppression of mast cell degranulation **[**61, 62**]**. Thus, the identification of opioid/opioid-receptor pathways in tendons implicates the potential for anti-inflammatory actions.

Mast cells, nerves, and tenocyte crosstalk

Tendon is a soft connective tissue where mast cells are found locally in the tendon proper, loose connective tissue close to the paratenon, muscle-tendon junction, or bone-tendon junction **[**14**]**. The tendon proper consists of tenocytes (tendon cells), which are fibroblast-like cells that are the basic cellular components of tendon tissue and are found uniformly aligned between collagen fibrils [63**]**. Tenocytes regulate the synthesis and degradation of extracellular matrix (ECM) components in response to internal and external stimuli to functionally adapt the tendon in response to altered levels of growth factors and mechanical load **[**64**]**. However, the most abundant cells in tendons are the tenocytes which can be activated by secreting various factors including cytokines, chemokines, and

nerve growth factor (NGF) [65-67] in either an autocrine or paracrine pathway and can also interact with cell-surface immune receptors and can be driven toward an inflammatory phenotype [11]. The inflammatory environment or tissue damage attracts macrophages and mast cells, which act in the front line of tissue immune defense. Increased accumulation of macrophages and mast cells has been detected in different phases of tendinopathy [68, 69]. The activated tenocytes together with accumulated inflammatory cells, i.e., macrophages and mast cells, initiate a coordinated cascade of released inflammatory mediators. The interactions between the inflammatory response and the extracellular matrix in the diseased tendon comprise a balance between reparation versus further degeneration within the tendon [15][69]. The exact role of mast cells in tendon pain and inflammation is intriguing. Activated mast cells have the capacity to secrete a wide panel of bioactive compounds [24, 25, 70]. Notably, several of these released compounds could potentially influence the neuro-inflammatory response by modulating pain signals from PNS to CNS. For example, mast cell-derived vascular- endothelial growth factor (VEGF), nerve growth factor (NGF), and brain – derived neurotrophic factor (BDNF), which are found in tendons, may contribute to neo-angiogenesis and nerve ingrowth [71, 72]. Thus, the nerve-mast cell axis can contribute to the regulation of nerve in growth in chronic tendon pain and inflammation.

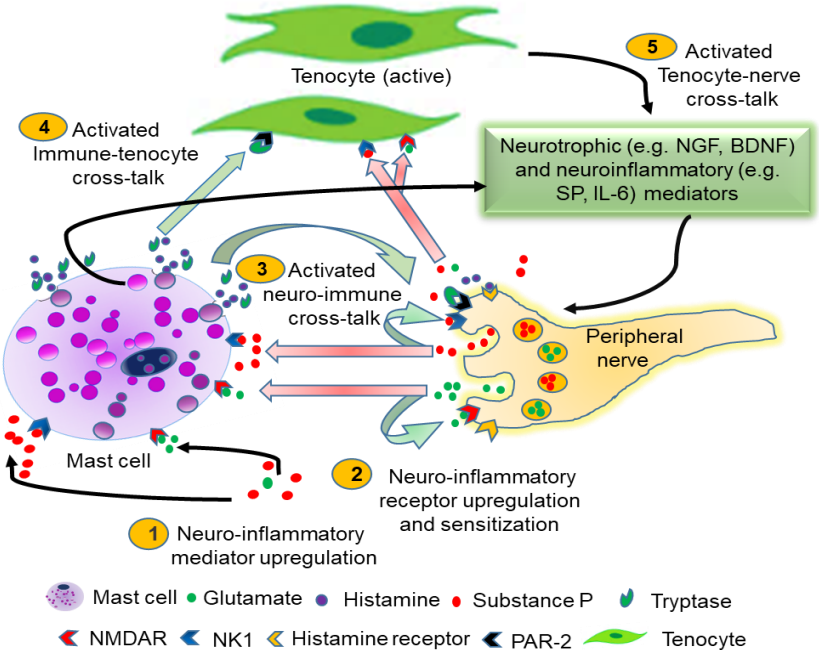

Figure 2. Schematic illustration of tri-directional crosstalk between mast cell, nerve, and tenocyte during inflammation and pain following a tendon injury. Peripheral nerve endings and tenocytes [82] can release neurotrophic and neuroinflammatory mediators including glutamate and substance P. Neurotrophic factors, such as nerve growth factor (NGF) [53] and brain- derived neurotrophic factor (BDNF), act on nerve endings causing nerve sprouting with nerve fiber ingrowth into the painful tendon proper.

Neuroinflammatory mediators, such as glutamate and substance P, may activate the immune system by autocrine and or paracrine pathway (specifically mast cells activation) [83], tenocytes, and peripheral nerve endings via their respective receptors, i.e., glutamate receptors (e.g., NMDAR1) and NK1-receptors. Activated mast cells release proteases, e.g., tryptase, which may functionally impact tendon cells or activate nearby nerves. Mast cells also release NGF, which furthermore stimulates neuro- inflammatory receptors (e.g., NMDR1) as well as neuro-inflammatory mediators (e.g., SP, glutamate) on peripheral nerves. Activated tenocytes moreover drive the production of neuro-inflammatory compounds (e.g., SP, NGF, IL-6). SP in turn may activate peripheral nerves (i.e., sensitization) via NK1 receptors in which NMDAR1 becomes activated (phospho-NMDAR1) and cause neurogenic inflammation [84, 85]. This figure was modified and adapted from Alim et al. 2020, 2022 [51]. NMDAR1, N-methyl-D-aspartate receptor type 1; NK1, neurokinin 1.

The close spatial connection of mast cells and peripheral nerve endings during healthy conditions in the tendon-surrounding structures, e.g., tendon sheath and bone-tendinous junction, suggests that mast cells can be activated by different neurotransmitters released from peripheral nerves in response to tendon injury or repetitive mechanical stress. In fact, repetitive mechanical tendon overload leads to increased release of sensory neuromediators, such as SP and glutamate [73]. Repetitive exercise of tendons leads to increased levels of, e.g., SP and CGRP receptors [63-65]. This increased release of SP and glutamate can activate their receptors (NK-1 and NMDAR1) on mast cells, leading to a pro-inflammatory cascade with the release of growth factors such as NGF and BDNF, which can initiate nerve sprouting and ingrowth in the tendon proper, i.e., interfascicular matrix. Neuromediator activation of mast cells can additionally lead to the release of cytokines and other pro-inflammatory mediators, which could contribute to the pathology of tendon pain [74-77]. Indeed, mast cells are known to respond to SP stimulation by secreting monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor (TNF-α), interleukin-8 (IL-8), IL-3, granulocyte–macrophage colony-stimulating factor, interferon-γ [78, 79] and histamine [80]. Moreover, mast cells were recently shown to respond to glutamate by secreting pro-inflammatory cytokines and chemokines [81]. The pro-inflammatory secretion from mast cells can act also in the opposite direction, i.e., to activate peripheral nerve cells. In addition to the effect of stimulating nerve ingrowth, their secretion of various mediators, e.g., histamine, serotonin, and dopamine, can activate the receptors expressed by neurons. In line with this consequence, the upregulation of histamine receptor 1 in nerve afferents may be involved in Moreover, serotonin and dopamine receptors are also expressed by peripheral nerve endings [84, 85], and may thus be involved in nerve sensitization. It has also been reported that mast cell tryptase can influence peripheral nerves by activating protease-activated receptor 2 (PAR- 2), expressed on the surface of

neurons [86, 87], suggesting peripheral nerve sensitization. Remarkably, tryptase expression is essentially restricted to mast cells [88, 89], and the activation of PAR-2 by tryptase is thereby a mast cell-dependent mechanism.

However, these scenarios are conceivable, there is still little firm evidence that such pathways are operative in vivo. In this review, we thus explored this fundamentally novel principle for how mast cells may communicate with nerve cells. In a previous report, we found that glutamate receptors were upregulated in an in vivo tendinopathy model known to evoke pain responses. Moreover, we found that glutamate receptors were to a large extent expressed by mast cells located within the injured tendon, whereas mast cells in non-injured tendons showed low/non-detectable glutamate receptor expression [14]. Prompted by these findings we hypothesized that glutamate might have an impact on mast cells, and here we evaluated this possibility. Intriguingly, we show that glutamate induces the expression of a panel of glutamate receptors on the mast cell surface. These findings have an important bearing on the mechanism of glutamate receptor induction/function in mast cells, implying that glutamate initially binds to glutamate receptors that are expressed at a low level on the mast cell surface, which in turn causes signaling that strongly amplifies the expression of the various glutamate receptors. Importantly, these findings provide evidence for a functional glutamate: glutamate receptor axis expressed by mast cells. Usually, this is in general agreement with the role of mast cells in other types of settings, e.g. allergic activation and in the defense against envenomation, where mast cells predominantly contribute at early stages, through mechanisms associated with rapid degranulation and actions of released granule mediators [90]. Altogether, the establishment of these neuro-immunological pathways suggests that the peripheral nervous system, in response to e.g., repetitive mechanical loading, injury, or metabolic activation, can intricately activate the innate immune system. Eventually, this could have an impact on nerve ingrowth, pain mediator release, and up-regulation of pain mediator receptors.

Glutamate signaling with pro/anti-inflammatory and transcriptional regulation in Mast cells.

We recently reported that glutamate exposure to mast cells which activates the expression of several proinflammatory and transcriptional genes. These included several inflammatory compounds, including IL-6, IL-13, CCL2, and CCL7 [3]. In addition, we also reported that glutamate induced the expression of the nuclear receptors Nr4a1 and Nr4a3, early growth response genes Egr2 and Egr3 as well as the transcription factors FosB in mast cells [3]. It is thus possible that signaling through the glutamate: glutamate receptor axis on mast cells can contribute to the inflammatory reaction that

escorts tendinopathy, inflammation, and other similar pathological settings. It may also be plausible that cytokines/chemokines released through such a mechanism can contribute, either directly or indirectly, to pain signaling and strong proinflammatory response.

However, our recent finding demonstrated a clear induction of FosB protein levels in both in vitro and in- vivo functional analysis **[**3, 15**]**. Therefore, we support this review by addressing the in vitro and in vivo significance of our findings, by focusing on the possibility that mast cells by glutamate and/or by injured tissue exhibit an upregulated expression of FosB and it's linked to glutamate: glutamate receptor axis (Fig. 3). Notably, FosB upregulation has implications for various processes including inflammation and tissue homeostasis as well as pain regulation. FosB regulation has also been demonstrated in various other cell types including tenocytes.

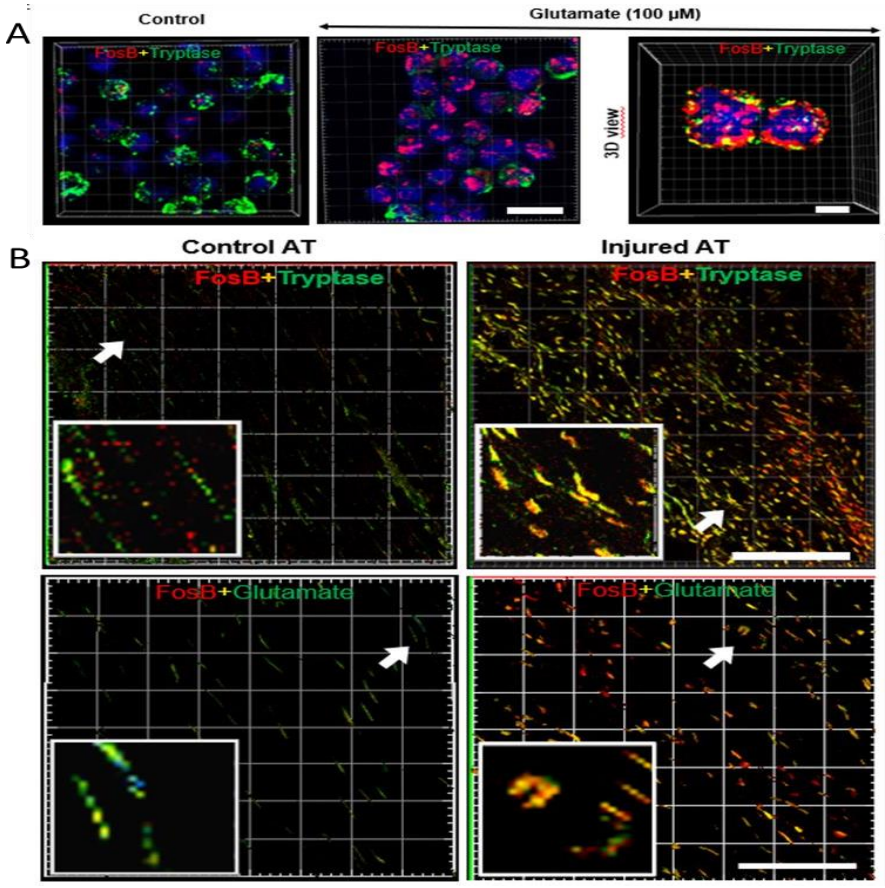

Figure 3. A) In-vitro visualization of FosB and mast cells tryptase in control- and glutamate-treated mast cells by confocal microscopy. Cells were constrained for FosB, tryptase (mast cell granule marker), and DAPI (nuclear marker). B) In-vivo colocalization of FosB, mast cell tryptase, and glutamate in an injured and control Achilles tendon (AT). **[**This figure was adapted and reprinted from Alim et al 2021**] [**3**]**

In addition to FosB, another study reported that Egr2 is upregulated in the injured tendon, which is in line with our current study demonstrated the upregulation of Egr2 in glutamate- stimulated mast cells. Therefore, we may establish a plausible scenario where an elevated level of glutamate receptor expression is induced after initial exposure of mast cells to glutamate released from neurons, followed by induction of FosB expression because of signaling events downstream of glutamate: glutamate receptor interaction. The downstream consequences of FosB upregulation most likely include activated transcription of target genes.

Possibly, FosB expression could thereby contribute to the induction of gene expression seen in glutamate-stimulated mast cells (Fig. 3). In agreement with this, a previous report suggested that Nrf1 in complex with FosB activates TNF expression in a murine mast cell- like cell line **[**91**]**. Furthermore, we reported that the induction of glutamate receptor expression was minimized by NMDAR-class glutamate receptor antagonists (e.g., MK-801, an ion channel inhibitor). These findings indicate that the induction of such genes may directly involve in the regulation of glutamate signaling via its receptors. In addition, our previous study noticed that MK-801 reduced the expression of pro-inflammatory responses that were triggered by glutamate stimulation **[**81**]** (Fig. 4). In line with this finding, we also reported that the glutamate receptor antagonist has a significant impact on abrogated the induction of early growth response gene and nuclear receptor/transcriptional factor gene (e.g., Egr2, Egr3, Nr4a3, and FosB) caused by glutamate signaling **[**3,15**]**.

Altogether, neuromediator signaling (especially glutamate/ SP/ FosB), and its various receptor involvement may develop as a potential therapeutic mechanism operative in tendon pain and inflammation.

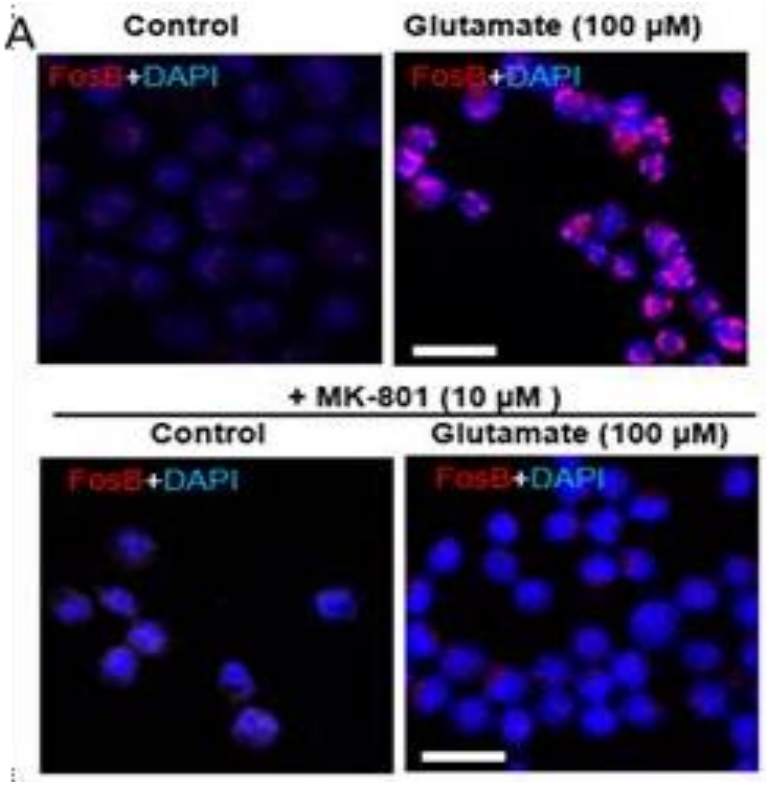

Figure 4. (A) Neuromediator signaling (glutamate) induced the expression of transcriptional factor FosB in mast cells than control and this effect was abrogated by glutamate receptor antagonists MK-801. **[**This figure was adapted and reprinted from Alim et al 2021**]**

Concluding remark

Altogether, this review summarizes a novel tri-directional axis by which neurons can interact with the immune cells and tendon cells. Future initiatives will be taken to evaluate if the glutamate: glutamate receptor axis expressed by mast cells potentially can be exploited for therapeutic purposes to ameliorate inflammatory/pain responses following tissue injury. Neuromediator signaling arises as one of the most pathways with a potential pathogenic mechanism operative in chronic tendon pain and inflammation after tissue injury. Strategies to target glutamate, SP, CGRP, and its receptors, which both are upregulated in tendon pain, healing response, and inflammation, could thereby represent potential therapeutic options in tendon disorders including inflammation and pain. However, glutamate receptors both ionotropic and metabotropic including other neuromediators/receptors have been highlighted in a multitude of chronic pain conditions. There are several potent NMDA-receptor antagonists available: MK-801, ketamine, methadone, memantine, amantadine, and dextromethorphan, which all are associated with side effects in the central nervous system.

Ways to overcome these side effects could include more specific druggable targets for the peripheral nervous system, which could be locally administered. Targeting the NMDA and NK1 receptor with specific antagonists could, in addition to having direct effects on pain transmission and inflammatory response in nerves, affect the NMDA receptor on mast cells and thereby hinder the degranulation-dependent release of sensitizing substances, as recently demonstrated in Achilles tendon **[**3, 14**]**. Furthermore, glutamate receptor targeting ion channel antagonists abrogated the responses of mast cells to glutamate, supporting the notion of functional glutamate: glutamate receptor axis in mast cells **[**3**]**. However, further studies are required to fully understand how neuromediators signaling are regulating the mast cells/tenocyte function and may influence pain and inflammation.

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