

● INVITED REVIEW

Neuronal changes resulting in up-regulation of alpha-1 adrenoceptors after peripheral nerve injury

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Abstract

Under normal conditions, the sympathetic neurotransmitter noradrenaline inhibits the production and release of pro-inflammatory cytokines. However, after peripheral nerve and tissue injury, pro-inflammatory cytokines appear to induce the expression of the alpha1A-adrenoceptor subtype on immune cells and perhaps also on other cells in the injured tissue. In turn, noradrenaline may act on up-regulated alpha1-adrenoceptors to increase the production of the pro-inflammatory cytokine interleukin-6. In addition, the release of inflammatory mediators and nerve growth factor from keratinocytes and other cells may augment the expression of alpha1-adrenoceptors on peripheral nerve fibers. Consequently, nociceptive afferents acquire an abnormal excitability to adrenergic agents, and inflammatory processes build. These mechanisms could contribute to the development of sympathetically maintained pain in conditions such as post-herpetic neuralgia, cutaneous neuromas, amputation stump pain and complex regional pain syndrome.

Key Words: alpha1-adrenoceptors; up-regulation; peripheral nerve injury; nerve growth factor; pro-inflammatory mediators; complex regional pain syndrome

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Introduction

After peripheral nerve injury, neutrophils, macrophages, T-cells and fibroblasts are recruited to the injured site and interact with resident cells such as mast cells, keratinocytes and dendritic cells (Reinke and Sorg, 2012; Li et al., 2013). Together, the migrating and resident cells release a cocktail of inflammatory mediators and growth factors that help to prevent infection and instigate tissue repair. However, these inflammatory mediators and growth factors can also disrupt sensory processing and, if left unchecked, may promote a cycle of chronic inflammation and pain (Schlereth et al., 2014). As reviewed below, the sympathetic nervous system might contribute to this cycle in a novel way.

α_1 -Adrenoceptors are up-regulated on nociceptive afferents that survive peripheral nerve injury

α_1 -Adrenoceptors are expressed on nociceptive afferent neurons both in the dorsal root ganglia (DRG) and on nerve fibers distributed to the skin (Dawson et al., 2011). Their functional role is yet to be fully established, but they appear to contribute to neurogenic vasodilatation both in rodents (Ren et al., 2005) and humans (Drummond, 2011). Furthermore, the sympathetic neurotransmitter noradrenaline lowers the temperature threshold of neurogenic vasodilatation during gradual local heating of the skin (Houghton et al., 2006), in

part by acting on adrenergic receptors (Hodges et al., 2008). Hence, under normal conditions, these receptors could play an active role in mediating vasodilator responses to thermal stimuli.

Findings from a number of sources indicate that expression of α_1 -adrenoceptors increases on nociceptive afferent fibers that survive peripheral nerve injury. For example, we recently found that α_1 -adrenoceptors were up-regulated after peripheral nerve injury on cutaneous nerve fibers labelled by nociceptive markers such as calcitonin gene-related peptide and isolectin B4 (Drummond et al., 2014a; Drummond et al., 2014b). Likewise, messenger RNA for the α_{1B} -adrenoceptor increased markedly in the DRG following peripheral nerve section or ligation of spinal nerves supplying those ganglia (Xie et al., 2001; Maruo et al., 2006). This may have functional consequences. For example, in cell culture studies on dissociated rodent DRG neurons, the proportion of cells that responded to noradrenaline increased markedly after chronic constriction injury of the sciatic nerve (Petersen et al., 1996). Similarly, cells in rat DRG infected with the varicella-zoster virus gained an unusual sensitivity to the α_1 -adrenoceptor agonist phenylephrine (Kress and Fickenschler, 2001; Schmidt et al., 2003). In additional studies, messenger RNA and binding sites for α_1 -adrenoceptors were elevated in the DRG in an animal model of painful diabetic neuropathy, and stimulation of α_1 -adrenoceptors aggravated pain behaviors (Lee et al., 2000).

Inflammatory mediators and growth factors may trigger this receptor up-regulation

Peripheral nerve and tissue injury results in Wallerian degeneration and causes the release of pro-inflammatory cytokines and growth factors (Thacker et al., 2007). This not only occurs around the injured nerve but also in the skin, DRG and associated areas in the central nervous system. Under normal conditions, noradrenaline inhibits the production and release of pro-inflammatory cytokines, such as interleukin 1 β (IL-1 β) and tumor necrosis factor- α (TNF- α), from immune cells by acting on beta-adrenergic receptors (Goyarts et al., 2008). However, after tissue injury, these inflammatory mediators induce the expression of the α_{1A} -adrenoceptor subtype on immune cells (Heijnen et al., 2002). To complete the loop, exposure to noradrenaline increases the production of the pro-inflammatory cytokine interleukin-6 (IL-6) in cells that express α_1 -adrenoceptors (Heijnen et al., 1996; Rouppe van der Voort et al., 2000; Perez et al., 2009). These receptors are expressed on epidermal dendritic cells (Seiffert et al., 2002), and also in inflamed lymphoid tissue and on circulating lymphocytes in patients with chronic inflammatory disease (Kavelaars, 2002). Thus, activation of aberrantly-expressed α_1 -adrenoceptors may contribute to chronic inflammation and pain.

Growth factors are also released after peripheral nerve and tissue injury. The prototypical neurotrophin, nerve growth factor (NGF), sensitizes nociceptors directly, and also undergoes retrograde transport to the cell nucleus where it induces the expression and post-translational modification of receptors and ion channels in the neural membrane (Reichardt, 2006). NGF evokes sprouting and regrowth of nerve fibers, hence assisting in the regenerative process. However, exposure to NGF can cause hyperalgesia (Lewin et al., 1993; Jankowski and Koerber, 2010), suggesting that the release of NGF may also contribute to neuropathic pain. In particular, NGF causes abnormal sprouting and an increased density of sympathetic nerve fibers in the skin and DRG. Abnormal sympathetic fibers were first observed in the DRG after ligation of spinal or sciatic nerves. In these animal models of neuropathic pain, sympathetic axons innervating the vasculature around the DRG sprouted and invaded the DRG after peripheral nerve injury, forming "baskets" of fibers around sensory neuron cell bodies (Chung et al., 1993; McLachlan et al., 1993; Ramer and Bisby, 1997). Abnormal sprouts of sympathetic nerve fibers were also observed in the skin after chronic constriction injury, intertwined with nociceptors (Yen et al., 2006). It is now known that hyperalgesia in response to NGF is at least partially mediated by sympathetic neurons as sympathectomy reduces the amount of hyperalgesia in response to NGF (Andreev et al., 1995).

In addition to directly sensitizing nociceptive afferents, NGF may evoke hyperalgesia by triggering the production of α_1 -adrenoceptors on peripheral nerve fibers. For example, in primary cultures of DRG neurons, exposure to NGF for 24 hours resulted in a two-fold increase in messenger RNA levels for the α_{1B} -adrenoceptor subtype, and receptor protein peaked 12 hours later (Zhang and Tan, 2011). The responsiveness of cultured DRG neurons to noradrenaline depended on whether the neurons expressed the NGF TrkA

receptor. Perfusion of neuronal cultures with noradrenaline increased the firing rate of TrkA-positive cells after exposure to NGF, but did not affect the firing rate of TrkA-negative cells. Thus, NGF may act upon DRG neurons to enhance the functional expression of α_1 -adrenoceptors and the excitability of these neurons to noradrenaline.

Other possible triggers of α_1 -adrenoceptor up-regulation include stress hormones such as adrenaline and corticosteroids, as the β_2 -adrenoceptor agonist terbutaline and the glucocorticoid dexamethasone induce the expression of α_{1B} - and α_{1D} -adrenoceptor messenger RNA and receptor protein in human monocytes (Rouppe van der Voort et al., 1999). However, whether these agents also trigger up-regulation of neural α_1 -adrenoceptors is unknown.

The keratinocyte layer forms part of an important barrier to the external environment that may be involved in sensory transduction and inflammatory reactions to injury. Keratinocytes can influence nociception by releasing substances that act on epidermal nerve fibers. For instance, the expression of voltage-gated sodium channels is elevated in the keratinocyte layer of patients with complex regional pain syndrome (CRPS) and post herpetic neuralgia (Zhao et al., 2008), and the inflammatory neuropeptide calcitonin gene-related peptide β appears to be raised in keratinocytes both in humans with CRPS and in various animal models (Hou et al., 2011). Human keratinocytes engrafted into an injured rat sciatic nerve increase the excitability of regenerating axonal sprouts in association with heightened production of NGF from the transplanted keratinocytes, and this results in chronic pain behaviors (Radtke et al., 2010). After tissue injuries such as tibial fracture, activation of neuropeptide and adrenergic receptors on the surface of keratinocytes triggers the proliferation of these cells and induces them to release inflammatory mediators and growth factors (Li et al., 2013). In turn, this may generate the up-regulation of neural α_1 -adrenoceptors and contribute to pain (Figure 1).

How this α_1 -adrenoceptor up-regulation might shape neural and tissue regeneration

Tissue repair progresses through an initial inflammatory stage, followed by a proliferative stage that lasts several weeks and a late remodelling stage where a scar is formed. α_1 -adrenoceptors may not only regulate the initial inflammatory stage (Kavelaars, 2002; Schlereth et al., 2014) but could also influence growth cycles *via* mitogen-activated protein kinase (MAPK) signalling pathways (Piascik and Perez, 2001), thus regulating cellular proliferation. In particular, the α_{1B} -adrenoceptor subtype mediates the proliferation of fibroblasts (Gonzalez-Cabrera et al., 2004), a key cell in the wound repair response as fibroblasts synthesize the extracellular matrix and secrete collagen. Stimulation of α_1 -adrenoceptors also enhances the migration of fibroblasts into wounds, thereby accelerating the rate of wound healing and scar remodelling (Sang et al., 2007; Taves et al., 2008; Wallert et al., 2011).

In the brain, α_1 -adrenoceptors increase the excitability of neurons and enhance the release of neurotransmitters from presynaptic terminals (Perez and Doze, 2011). The α_{1A} -subtype appears to be involved in neurogenesis, and mediates the proliferation and migration of neural progenitor and stem

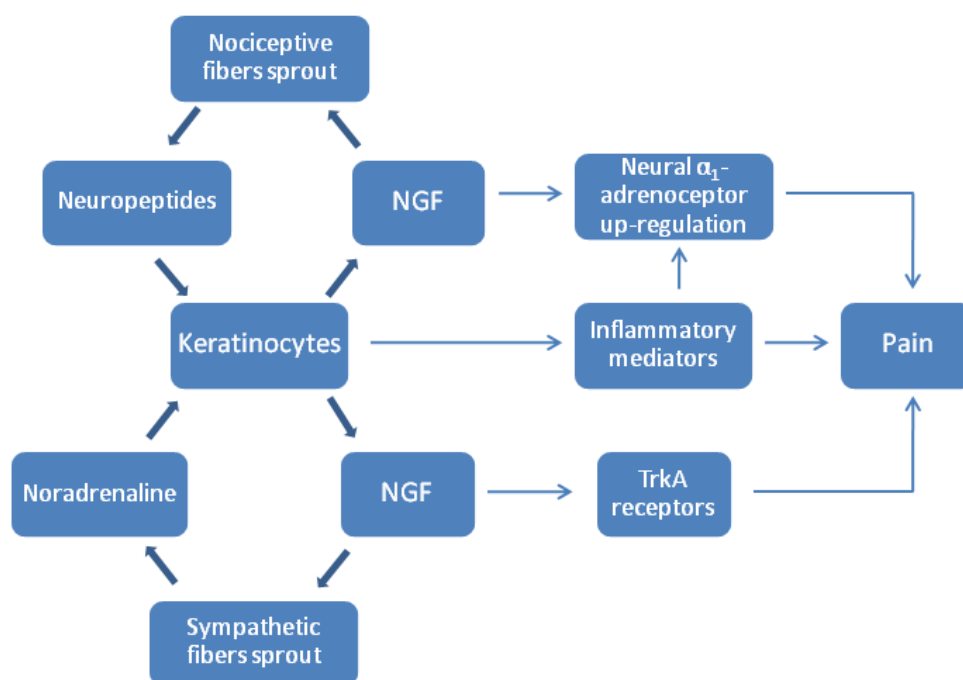


Figure 1 Proposed model for an involvement of keratinocytes in the generation of chronic pain after peripheral nerve injury.

Injury-evoked release of neuropeptides from cutaneous nociceptive afferents triggers the production in keratinocytes of inflammatory mediators such as tumor necrosis factor (TNF) and interleukin-6 (IL-6), and growth factors such as nerve growth factor (NGF) (Li et al., 2013; Birklein et al., 2014). These agents not only induce pain sensitization but also augment the expression of α_1 -adrenoceptors on nociceptive afferents. In turn, stimulation of these α_1 -adrenoceptors provokes pain. As well, NGF generates axonal sprouting of nociceptive afferents and sympathetic efferents, thereby heightening levels of cutaneous neuropeptides and noradrenaline. These neuromodulators act on keratinocytes and nociceptive afferents to perpetuate the cycle.

cells, whereas the α_{1B} -subtype may be involved in neurodegeneration (Perez and Doze, 2011). Whether these α_1 -adrenoceptor subtypes contribute to neural regeneration and/or migration after peripheral nerve injury is yet to be explored.

Clinical implications

The increase in α_1 -adrenoceptor expression after nerve and tissue injury could have important clinical implications in neuropathic pain syndromes. In humans, intradermal administration of noradrenaline and other α_1 -adrenoceptor agonists generally provokes only momentary pain. Nevertheless, injecting these adrenergic agents into symptomatic regions intensifies pain in certain neuropathic syndromes (Davis et al., 1991; Chabal et al., 1992; Torebjork et al., 1995; Choi and Rowbotham, 1997; Ali et al., 2000; Mailis-Gagnon and Bennett, 2004; Lin et al., 2006), consistent with an aberrant adrenergic influence on nociception. In patients who develop CRPS after peripheral nerve injury, the heightened sensitivity to adrenergic agents may be accompanied by an increased expression of α_1 -adrenoceptors on cutaneous nerves and keratinocytes in the painful limb (Drummond et al., 2014b).

In summary, a major early component of neuropathic pain is infiltration of immune cells into the injured tissue that release inflammatory mediators. These mediators could either directly, or through the induction of neurotrophic factors, trigger increased α_1 -adrenoceptor expression on neurons and other cells around the site of injury. In turn, activation of α_1 -adrenoceptors on fibroblasts and keratinocytes may trigger further release of growth factors and inflammatory mediators. Thus, an upward spiral of α_1 -adrenoceptor expression on these cells and on regenerating neurons could

engender an adrenergic component of inflammation and pain. If so, blocking the α_1 -adrenoceptor might prove to be a useful therapeutic strategy for patients with an adrenergic component of neuropathic pain.

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