Neuropathic pain and its treatment with ARA 290 and ketamine : overlapping pathways

Swartjes, M.

Chapter 1

Introduction

Neuropathic pain

Pain serves as a warning for the body of potential damage from a noxious stimulus and allows for appropriate measures to avoid irreversible damage. Physiological pain is directly correlated to the noxious stimulus, i.e. if the stimulus persists, the pain persists and if the stimulus dissipates, the pain dissipates. Neuropathic pain, however, is a maladaptive response to lesions arising from the nervous system following trauma (e.g. accident, surgical), toxicity (e.g. cisplatin) or systemic disease (e.g. diabetes mellitus, sarcoidosis). This type of pain is often chronic in nature and is no longer correlated to the initial stimulus, i.e. the pain persists after the initial stimulus has dissipated or the pain is experienced in an exaggerated form.[1] These exaggerated pain perceptions include thermal and mechanical allodynia (a non-painful stimulus is perceived as painful, e.g. cold intolerance or the rubbing of clothes) and hyperalgesia (a painful stimulus is perceived as more painful).[2] Regardless of the underlying cause of chronic neuropathic pain, this disease causes great disability in everyday life and often results in the inability to maintain a job or in reduced social participation.[3] In addition, it is a disease that is difficult to treat with conventional pain medication and is often empirically treated with antidepressants and antiepileptics[4] with variable efficacy and often intolerable side effects. The mechanism of the development of neuropathic pain, regardless of the underlying cause, is diverse and includes intertwined and converging pathways such as inflammation, loss of peripheral nerve fibers, N-methyl-D-aspartate (NMDA) receptor upregulation and glia involvement.[5] Targeting either of these targets has provided ample evidence of neuropathic pain relief or disease modification suggesting involvement of one or more of these targets.

Inflammation

The body responds to pathogens or tissue damage with an inflammatory reaction, aimed at preventing infection with a pathogen, or the removal of debris after damage. Tissue damage to a peripheral nerve induces an inflammatory reaction characterized by the release of inflammatory mediators, such as cytokines (e.g. interleukins, tumor necrosis factor α: TNF-α)[6-8] that recruit more immune cells or destroy damaged cells. These cytokines are released by residing and recruited immune cells (e.g. macrophages, T-cells) or support cells (e.g. Schwann cells). Alternatively, many systemic diseases such as diabetes mellitus or sarcoidosis induce local or systemic inflammatory processes. Local inflammatory reactions after nerve damage have their effect in the peripheral nerve by providing an environment of constant noxious

stimuli resulting decreased thresholds for signal transduction (i.e. decreased depolarization thresholds) resulting in enhanced pain signaling. This barrage of signals induces central sensitization in the spinal cord[9], lowering the threshold at which neurons depolarize, causing an altered perception of pain[10]. Alternatively peripheral nervous system inflammation can result in retrograde transport of TNF-α to the central nervous system expanding the inflammatory reaction to the central nervous system, resulting in cytokine release in the dorsal horn[11]. Alternatively the central nervous system can become inflamed either by retrograde transport of cytokines, like TNF-α, or local inflammatory reaction[12] by resident nervous system immune cells (i.e. microglia) or support cells (i.e. astrocytes)[13], which will be discussed in the following paragraphs.

Microglia

Microglia are the resident macrophages of the central nervous system and over the years, this cell type has been correlated to neuropathic pain states arising from various types of lesions[14] and has become an interesting target for pharmacological treatment[15] of neuropathic pain. It has been shown that these cells become activated by various inflammatory cytokines (TNF-α, interleukins)[16] and chemokines (e.g. chemokine (C-C motif) ligand 2: CCL2, also known as macrophage chemoattractant protein 1: MCP-1)[17;18], cytokines and chemokines that are released after nerve damage. Their phenotype changes from resting (i.e. ramified with a small soma) to activated (i.e. amoeboid, retracted rami and a thickened soma)[19]. Additionally, intracellular signaling pathways such as the P38 mitogen activated protein kinase (P38-MAPK)[20], janus kinase-signal transducer and activator of transcription (JAK-STAT)[21] involved in the regulation of transcription factors for, for instance the production of cytokines, become phosphorilyzed increasing cytokine production and release, creating a self-sustained inflammatory process contributing to neuropathic pain.

Astrocytes

Astrocytes are the support cells of the central nervous system and make up for the blood to central nervous system barrier. After peripheral nerve injury, astrocytes are activated in the spinal cord, in response to inflammatory mediators (e.g., TNF-α)[22]. Astrocyte activation may manifest as the phosphorylation of several intracellular signaling pathways and proliferation of these cells (i.e. astrogliosis)[23]. Activation of the intracellular signaling pathways results in the production of inflammatory

cytokines and chemokines (e.g., interleukin-1β: IL-1β and MCP-1)[22]. These mediators can lead to enhanced pain states by acting at both presynaptic sites on primary afferents and post-synaptic sites on dorsal horn neurons causing increased excitation and decreased inhibition of spinal cord nociceptive neurons[24].

Loss of peripheral small nerve fibers

Systemic diseases (diabetes mellitus and sarcoidosis), critical illness neuropathy (due to sepsis or multi organ failure resulting in prolonged intensive care unit stay) as well as pain syndromes such as fibromyalgia are associated with the loss of the small sensory fibers in the epidermis of the skin: small fiber neuropathy (SFN) and subsequent neuropathic pain[25-28]. SFN may result from a continuous inflammatory state of the peripheral nerves innervating the skin with infiltration of immune cells, cytokine production and degeneration of the nerves and thereby contributing to sensory deficits, such as dysesthesia or pain.

The N-methyl-D-aspartate receptor

Glutamate is the central nervous system's major neurotransmitter that acts on the NMDA receptor. This receptor consists of two obligatory NR1 subunits that can be coupled to either two NR2A through D or two NR3A through B subunits to yield a functioning receptor (e.g. $NR1_2/NR2A_2$ configuration). Activation of the NMDA receptor by glutamate results in the removal of the physical magnesium ion block that seals the receptor, resulting in an influx of calcium ions, allowing depolarization of the nerve and signal transduction (reviewed in[29]). In neuropathic pain states, the NMDA receptor becomes upregulated in the dorsal horn, increasing synaptic transmission and contributing to exaggerated pain states such as allodynia and hyperalgesia[30]. The NR2A containing NMDA receptors are ubiquitously distributed throughout the brain and spinal cord, while the NR2B containing NMDA receptors are restricted to areas specific for pain signaling, i.e. laminae I and II of the spinal cord dorsal horn and thalamus[31]. The NR2B receptor subunit has been positively correlated to various pain states, including inflammatory[32] and neuropathic pain[31].

The innate repair receptor

Erythropoietin (EPO) is involved in the genesis of red blood cells. Hypoxia induces stabilization of hypoxia inducible factor 1α (HIF-1α) resulting in the transcription of EPO. EPO, in turn, activates the erythropoietin receptor dimer ($EPOR_2$) present on hematopoietic cells, resulting in increased survival of erythroblasts. Alternatively, erythropoietin possesses anti-inflammatory properties by acting as a natural antagonist of TNF-α through a different receptor configuration: EPOR-β-common-receptor (EPOR-βcR), termed the innate repair receptor (IRR) (reviewed in[33]). This βcR consist of the β chains of the granulocyte-macrophage colony-stimulating factor (GM-CSF)/ interleukin 3/interleukin 5 receptors, commonly utilized by type 1 cytokines involved in the innate and acquired immunity (reviewed in[34]). Activation of the IRR by endogenous or recombinant EPO results in attenuation of the immune response, increased survival of tissue, and enhanced regeneration, thus tissue protection and tissue repair[35-38].

Treatment

Currently, chronic neuropathic pain is treated according to the following algorithm with variable results. Current guidelines recommend pharmacological treatment with antidepressants (amitryptiline) followed by antiepileptics (carbamazepine and gabapentin), opioids (tramadol) or topical capsaicine[4]. Treatment with these drugs is often inadequate resulting in insufficient pain relief and is accompanied by side effects that may be severe and intolerable.

Treatment with NMDAR antagonists

Over the past few years, ketamine has gained interest as a pharmacological treatment for chronic neuropathic pain[39]. A relatively short treatment paradigm induces long-term relief of neuropathic pain symptoms in complex regional pain syndrome type 1 patients[40]. The treatment with ketamine, however coincides with undesirable and intolerable side effects, such as nausea, dizziness, anxiety and psychosis. Ketamine is a non-selective NMDAR antagonist, targeting all the NMDAR subtypes, some of which may be involved in the observed side effects. It is unclear, however, if ketamine or its active metabolite norketamine is responsible for the pain relief and/or induced side effects. NMDA receptor antagonists that are specific for the more pain specific NR2B subunit are being developed, one of which is Traxoprodil (CP-101,606) which is devoid of psychomimetic side effects[41] and may be effective in pain relief.

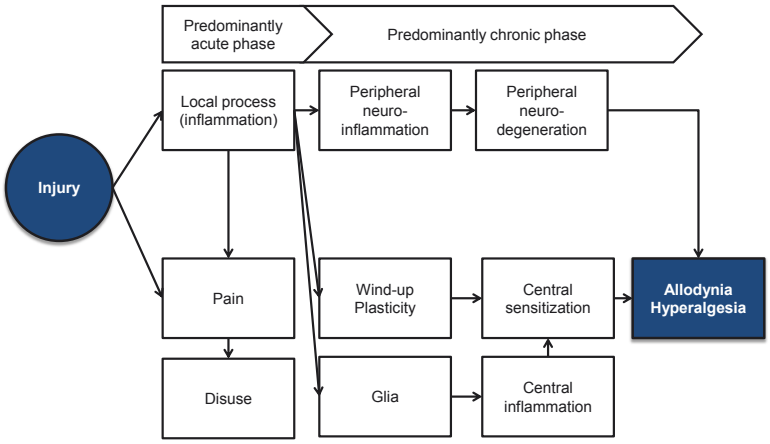

Figure 1: Schematic representation of the current understanding of the development of neuropathic pain.

Rationale for treatment with ARA 290

Inflammation is an important part of the mechanism in the onset and maintenance of neuropathic pain. Counteracting the inflammatory response with EPO has proven to be effective in several types of injury, including injuries to the nervous system. However, EPO induces hematopoiesis as an undesired effect to the tissue protective and regenerative properties. Therefore, derivatives of EPO that are tissue protective but not hematopoietic have been developed[42], one of which is the small helix B peptide ARA 290. This linear 11-amino acid peptide is a representation of the amino acids of EPO interacting with the EPOR and has tissue protective effects equal to EPO, but without hematopoietic effects[43]. Treatment with ARA 290 may be effective in treating or preventing neuropathic pain after nerve injury induced neuropathic pain.

Aims

The experiments described in this thesis were designed to investigate:

- The treatment of neuropathic pain with ARA 290
- The treatment of neuropathic pain with NMDAR antagonists ketamine, norketamine and Traxoprodil
- The overlapping pathways of ketamine and ARA 290 in the treatment of neuropathic pain
- The feasibility of CCM as an objective measure of small fiber neuropathy in sarcoidosis patients with neuropathic pain
- The effect of treatment with ARA 290 on pain and nerve fiber density in patients with sarcoidosis and painful small fiber neuropathy

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