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Pathophysiology of the constant burning, tingling element of neuropathic pain: A new hypothesis

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ABSTRACT

Neuropathic pain (NPP) presents itself with at least one of the following elements: constant, intermittent and evoked pain. The pathophysiology of NPP is still controversial, in especial of its constant element, the focus of this study. Many hypotheses have been proposed in an attempt to explain it, but none of them seems to account for the various aspects of the constant element of NPP. Under the phylogenetic perspective, it is postulated, the pain may be classified into two categories: paleopain, present in inferior animals, poorly localized, transmitted by the medial pain system pathways, and neopain, conducted by the lateral pain system pathways, very well localized, described in terms suggestive of tissue damage and present in superior animals. We believe that, in humans, under physiological circumstances, the expression of the paleopain was completely abolished. It is proposed that it is due to the tonic inhibition of the medial thalamus by the ventral posterior (VP) nucleus of the thalamus, via a circuit that the authors described and named prosencephalomesencephalic modulatory circuit (PMMC). Two pathways are suggested as activators of the PMMC: the neospinothalamic/neotrigeminothalamic and ventral spinothalamic tracts. The interruption of this circuit or of its activators, at any point, would lead to the release of the medial thalamus from the inhibitory influences of VP, allowing the manifestation of the paleopain. It is postulated that the constant burning, tingling element of NPP is nothing more than the clinical expression of the paleopain. Evidence to support this hypothesis is provided. As a direct consequence of the presented hypothesis, the substantia nigra pars reticulata is proposed as a new target of deep brain stimulation for the treatment of the constant burning, tingling element of NPP.

Introduction

Neuropathic pain (NPP), also known as neural injury pain, central pain or deafferentation pain, is a chronic pain resulting from a lesion, of any etiology, inflicted on the central or peripheral nervous system [41,49,51–53,63,65–70].

It affects about 1% of the world population [71] and has a significant negative impact on one's quality of life, functional domains and work capacity [40].

Clinically, it presents with at least one of the following elements: (1) Constant pain: found in practically all cases, it is spontaneous (independent of peripheral stimuli) and more commonly described as a burning or tingling sensation and, less frequently, as a cold sensation or aching; (2) Intermittent pain: also spontaneous, frequently described as an electric shock, shooting, stabbing or sharp sensation that lasts from a few seconds to a few minutes and usually occurs several times a day; it is rare after brain lesions, but frequent in patients with pain resultant from peripheral nervous system or spinal cord injury; (3) Evoked pain: it depends on external stimulation and can be expressed as allodynia or hyperpathia; although it may occur following lesions inflicted in any part of the somatic nervous system, in our experience, it is more frequent after brain lesions [54,55,65–70].

Under a surgical perspective, the intermittent and evoked elements generally respond to the same strategies adopted for treating nociceptive pain, that is, interruption (neurotomy, posterior rhizotomy, anterolateral cordotomy etc.) or modulation

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(periventricular-periaqueductal gray matter deep brain stimulation and intrathecal infusion of opioids) of the neospinothalamic (NSTT)/neotrigeminothalamic (NTTT) tracts. The constant pain, on the other hand, although it may be temporarily relieved by proximal anesthetic blocks, is generally aggravated by NSTT/NTTT interruption. Furthermore, it is not usually relieved by modulation of the NSTT/NTTT pathways. Fortunately, it may respond to other neuromodulatory procedures, such as the electrical stimulation of peripheral nerves, Gasserian ganglion (facial NPP), spinal cord, medial lemniscus, ventral posterior nucleus of the thalamus – VP (ventral posterolateral nucleus + ventral posteromedial nucleus; also known as ventrocaudal or ventrobasal nucleus), internal capsule, and motor cortex. Curiously, such procedures are usually inefficient to treat the intermittent and evoked elements of NPP as well as nociceptive pain [49,51–53,55,65–67,69,70].

The intermittent pain occurs in areas that are partially – but not completely – deafferented and can be alleviated by complete interruption of the NSTT/NTTT tracts, suggesting that it is transmitted by these pathways. Apparently, it is generated at the lesion site, either by irritation of the these tracts by local scarring or by ephapse [49,51–53,63,65–70].

Similarly to the intermittent pain, the evoked pain also occurs only in areas that are partially – but not completely – denervated and can be abolished by the complete interruption of the NSTT/NTTT, suggesting that it is also transmitted through these pathways. Unlike the intermittent pain, which is spontaneous in nature, however, it depends on the peripheral activation of mechanoreceptors or nociceptors. The impulses generated in these receptors, due to synaptic rearrangements resultant from neural damage, would be abnormally processed in the central nervous system, causing this pain modality. Upon nociceptive deafferentation, a series of alterations occurs downstream of the lesion site: degeneration of the presynaptic terminals, profuse branching of the remaining afferents, replacement of inhibitory synapses by excitatory ones, increase in effectiveness of formerly poorly effective synapses, activation of previously inactive synapses and reinnervation of deafferented nociceptive neurons by thick (Aα and Aβ) or thin (Aδ) myelinated or unmyelinated (C) fibers. In this scenario, the activation of mechanoreceptors would trigger the allodynia (mechanoreceptors → thick myelinated fibers → nociceptive cells), while the activation of nociceptors would produce the hyperpathia (nociceptors → excess of thin myelinated and unmyelinated fibers → nociceptive cells) [49,51–53,63,67,69,70].

Even more controversial is the pathophysiology of the constant pain. Several hypotheses have already been proposed trying to explain it [41,51,52]. However, all of them have important limitations [52]. Apparently, the only fact accepted indiscriminately, by the vast majority of authors, is that the lesion of the NSTT or NTTT is *sine qua non* for its emergence [41,49,51–53,63,65–70].

Vilela Filho, in an attempt to clarify the mechanisms involved in the pain relief produced by VP deep brain stimulation (DBS), proposed that it is due to the activation of a polysynaptic pathway, which he subsequently named as prosencephalomesencephalic circuit – PMC [62]. This circuit will be reviewed in detail afterwards.

In the present study, the authors make some modifications to the PMC previously described, proposing that it acts, under physiological conditions, as a center for pain suppression, and put forward the hypothesis that the constant element of NPP, the focus of this study, results from the disinhibition of the medial thalamus (MT – intralaminar and dorsomedial nuclei) and subsidiary circuit (which is here first described), due to the hypoactivity of the PMC or of its activators (NSTT/NTTT) and, probably, the ventral spinothalamic tract – VSTT as well). Evidence to support this hypothesis is provided.

Evolution of the hypothesis

Pain modulation and mechanisms involved in pain relief produced by VP electrical stimulation

The first pain modulatory system (gate control theory) was described by Melzack and Wall, in 1965. According to these authors, thick myelinated fibers would excite inhibitory interneurons of the substantia gelatinosa which, in turn, would inhibit nociceptive afferents, preventing them from exciting the nociceptive projection neurons, closing the pain gate [35]. The nociceptive afferents (thin myelinated and unmyelinated fibers), on the other hand, would simultaneously inhibit these inhibitory interneurons and excite the nociceptive projection neurons, opening the pain gate [35]. Based on this principle, Wall and Sweet, in 1967, and Shealy et al., in the same year, clinically introduced electrical stimulation of the peripheral nerves and of the spinal cord, respectively, for the treatment of pain [47,72].

Another important modulatory system was later proposed by Reynolds, who demonstrated that the electrical stimulation of the periaqueductal gray matter (PAG) produced profound analgesia in rats [43]. A series of posterior studies demonstrated that this analgesia depended on the intermediate activation of nuclei of the dorsolateral pontine tegmentum (locus coeruleus and subcoeruleus) and of nuclei of the rostroventral medulla (nucleus raphe magnus, nucleus reticularis magnocellularis, nucleus reticularis gigantocellularis, and nucleus reticularis paragigantocellularis lateralis), from which, respectively, noradrenergic and serotonergic descendent inhibitory pathways originate, coursing through both dorsolateral funiculi of the spinal cord, to inhibit dorsal horn nociceptive neurons. It was also demonstrated that the stimulation of the periventricular gray matter (PVG) produced the same effects of the stimulation of the PAG and that both were interconnected [4–7,11,21,33,61].

A variety of surgical procedures have been used for treating NPP, specially the neuromodulatory techniques, such as the electrical stimulation of peripheral nerves, Gasserian ganglion, spinal cord, medial lemniscus, VP, posterior limb of the internal capsule, motor cortex, and PVG-PAG [1,25,38,42,44,47,54,55,60,64–67,69,70].

PVG/PAG-DBS was first performed in humans by Richardson and Akil, in 1977 [44]. Unilateral activation of this structure promotes bilateral pain relief. It may be used for treating nociceptive pain and the intermittent and evoked components of NPP. Its mechanism of action has already been clarified.

VP-DBS, clinically introduced by Mazars et al., has been used since the 1960's, and is indicated for treating the constant element of NPP [25,34,52–55,58,59,61,62,64–67,69,70]. Its activation provides relief of the contralateral pain exclusively. However, the way this occurs has not yet been clearly established.

Several hypotheses have been put forward in an attempt of explaining the pain relief produced by VP-DBS.

According to one of the most accepted hypothesis, defended by Tsubokawa et al. [58,59] and Willis et al. [74], among others, VP stimulation would antidromically excite NSTT collaterals given off to the rostroventral medulla which, in turn, projects inhibitory descending axons through both dorsolateral funiculi of the spinal cord to the dorsal horn nociceptive neurons. This pathway corresponds to part of that one proposed for the inhibition of dorsal horn nociceptive neurons by means of PVG/PAG-DBS.

According to Gerhart et al. [22], VP stimulation, via medial lemniscus, would antidromically activate neurons in the dorsal column nuclei, where there is a small but significant number of cells that sends axons both to VP and to the spinal cord, which seem to