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Review Article

Dorsolateral prefrontal cortex sensing analgesia

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Chronic pain often has an unknown cause, and many patients with chronic pain learn to accept that their pain is incurable and pharmacologic treatments are only temporarily effective. Complementary and integrative health approaches for pain are thus in high demand. One such approach is soft touch, e.g., adhesion of pyramidal thorn patches in a pain region. The effects of patch adhesion on pain relief have been confirmed in patients with various types of pain. A recent study using near-infrared spectroscopy revealed that the dorsolateral prefrontal cortex (DLPFC), especially the left side, is likely to be inactivated in patients experiencing pain relief during patch treatment. Mindfulness meditation is another well-known complementary and integrative approach for achieving pain relief. The relation between pain relief due to mindfulness meditation and changes in brain regions, including the DLPFC, has long been examined. In the present review article, we survey the literature describing the effects of the above-mentioned complementary and integrative treatments on pain relief, and outline the important brain regions, including the DLPFC, that are involved in analgesia. We hope that the present article will provide clues to researchers who hope to advance neurosensory treatments for pain relief without medication.

Key words: chronic pain, complementary and integrative treatment, mindfulness, near-infrared spectroscopy, pyramidal thorn patch

Significance

The involvement of the dorsolateral prefrontal cortex (DLPFC) in pain is well known. Our studies showed that application of pyramidal thorn patches to pain regions decreased the degree of pain, leading to a lower oxyhemoglobin level in the DLPFC. Mindfulness meditation is another well-known complementary and integrative approach for achieving pain relief. The relation between pain relief due to mindfulness meditation and changes in brain regions, including the DLPFC, has long been examined. We introduce the effects of these complementary and integrative treatments on pain relief, and outline the important brain regions, including the DLPFC, that are involved in analgesia.

Introduction

People with chronic pain often suffer from debilitating conditions with high social and economic costs. In many cases, the cause of the pain is unknown, and the effectiveness of pharmacologic treatments may be limited. One perspective of pain management is that fundamental therapeutic methods are not useful, and methods should be targeted at extinguishing

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or at least alleviating pain. That is, patients with chronic pain will feel some relief if they can forget the pain. Many patients seek complementary and integrative health approaches to achieve relief, including massage, meditation, and ingestion of herbs, not only in Asian countries but all over the world. The National Center for Complementary and Integrative Health in the USA reports that tens of millions of people with the musculoskeletal pain (e.g., back pain, neck pain, joint pain, etc.) currently use complementary and integrative medicines [1].

From the viewpoint of neuroscience, it is important to determine which brain regions are activated/inactivated for analgesia. Recent publications have pointed out the relationship between pain/pain relief and an activation change in the dorsolateral prefrontal cortex (DLPFC), especially by using the analgesic treatments of repeated transcranial magnetic stimulation (rTMS) and transcranial direct or alternating current stimulation (tDCS or tACS) [2–9], even though there was a report showing that tDCS was no more effective than a placebo treatment for fibromyalgia [10]. A study using an electronic wrist-ankle acupuncture showed an analgesic effect accompanied with the inactivation of DLPFC [11].

As a tool for the detection of activation/inactivation of the brain regions for analgesia, functional magnetic resonance imaging (fMRI) is usually used, because blood flow in a specific brain region increases due to the coupling between the neuronal activation and brain blood flow [12]. Although fMRI is a complex method with fine spatial and temporal resolutions, a weak point is that experimental participants must assume a supine position. The supine position is thought to induce large changes in the autonomic nervous system [13]. Furthermore, fMRI is costly and noisy compared to other brain imaging methods. Therefore, a more suitable apparatus is needed for studies of analgesia. Near-infrared spectroscopy (NIRS) also reveals the coupling between neuronal activation and brain blood flow. NIRS detects changes in the absorption of near-infrared light reflecting oxyhemoglobin and deoxyhemoglobin levels, and clarifies the local change in blood flow in the brain [14]. The advantage is that the experimental participants can maintain a sitting or standing position while being assessed using NIRS [15]. NIRS is a reasonable cost and the operating noise is silent. A limitation of the use of NIRS is that it can only obtain information of blood flow due to the activation/inactivation of neurons relatively close to the brain surface (within 2 to 3 cm deep).

In the present article, we review the effects of the adhesion of pyramidal thorn patches as one of complementary approaches for pain relief and the observed changes in brain regions using NIRS during the experience of pain relief. In particular, we discuss the activation/inactivation of dorsolateral prefrontal cortex (DLPFC). In addition, mindfulness meditation is introduced as another complementary approach for pain relief, and the brain regions that change during pain relief as observed with fMRI are compared with those observed during the above-described patch treatment. Finally, to explore the molecular mechanisms of pain relief, we consider the neuropeptide oxytocin as a candidate analgesic agent [16].

Patch Treatment for Pain Relief: NIRS Study

Adhesion of pyramidal thorn patches to pain regions for pain relief was proposed by Saito and colleagues [17,18]. They have reported the effectiveness for 300 patients of pyramidal thorn patch adhesion on pain regions as a complementary medicine [18]. The pyramidal thorn patch is a circular adhesion patch made of synthetic resin that is 3 cm in diameter and 0.1-mm thick. The center of the circular patch is constructed from low-density polyethylene in a 7-mm square area and the tapered pyramidal thorn is 3 mm high (Figure 1). The operator presses the skin of the participant (i.e., patient), where the participant feels the pain, with a small metallic stick, because the participants who the operator sees have only somatic pains.

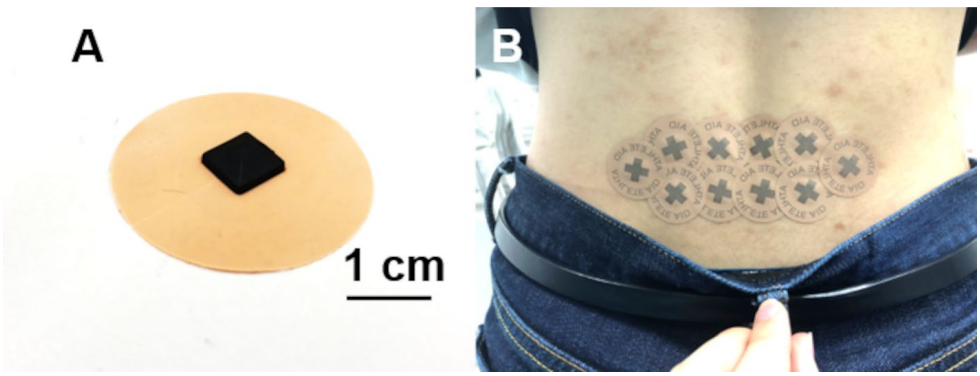

Figure 1 Pyramidal thorn patch. (A) The pyramidal thorn patch has a diameter of 3 cm and a thickness of 0.1 mm, and the tapered pyramidal thorn constructed from low-density polyethylene is 3 mm high and 7-mm square. (B) Application of pyramidal thorn patches to a pain region (e.g., lower back). After palpating to determine the pain region, several pyramidal thorn patches were applied to alleviate the pain. Reprinted from [21] under a CC BY license.

Studies that evaluate changes in the degree of pain generally use methods to express the data numerically. The conventional method of expressing the data numerically is to apply a visual analog scale (VAS) [19]. In a VAS scale, a score of 0 is usually defined as feeling no pain at all, whereas there is some ambiguity in assigning the remaining values to the define the degree of pain. To overcome this problem, the use of transcutaneous electric stimulation (TCES) has been recommended [20]. The values measured in TCES indicate the 'pain degree', which can be calculated from the current perception threshold, defined as the lowest electrical current detected by participants, and the pain-compatible electrical current, defined by the electrical current judged by each experimental participant to be compatible with the intensity of the ongoing pain. The usefulness of TCES for pain relief has also been confirmed [21].

Application of the pyramidal thorn patches to various pain regions in 300 patients relieved the pain in almost all the patients within 4 treatments [18]. The decrease in pain induced by patch adhesion was observed by both VAS and TCES [18,21]. The patches were repeatedly applied until the participant states that the pain disappeared. The pain region moved discontinuously along the nerve fibers before disappearing. This movement was called 'virtual movement of the pain region'. Several patches were applied in the virtual pain region, which discontinuously moved on the skin. This pain movement was recognized by the participants themselves. Thus, when the participant reported that the pain region was moved by patch application, the operator observed the movements. The presence or absence of pain depended on the feeling of the participants (i.e., self-reported pain) [18]. We do not know why this phenomenon occurred, but it is consistent with the cutaneous rabbit illusion, in which sensory stimulation delivered to one region and then to a more proximal region in the same vicinity evokes the perception of hopping stimuli [22].

The neurophysiological basis of the analgesic effects induced by the pyramidal thorn patch against pain has been thought as follows [18]. In pathological pain, including joint and muscle pain [23], the pain signal appears in the normal peripheral tissue and in nerves that activate Aδ fiber high-threshold mechanoreceptors and C fibers [24]. This pain signal is considered to be reduced by gentle physical stimulation of the skin (e.g., application of pyramidal thorn patches) that activates Aβ fiber low-threshold mechanoreceptors [24,25]. The interaction between the nociceptive signal (Aδ and C fibers) and the non-nociceptive signal (Aβ fibers) was introduced as the gate control theory of pain [26,27]. The gate control theory hypothesizes that non-nociceptive input closes the gates to nociceptive input, which prevents pain sensations from traveling to the central nervous system. Therefore, Aβ fibers inhibit the effects of the firing of Aδ and C fibers. The pain seems to be decreased when the area is rubbed by the application of pyramidal thorn patches, because the activation of non-nociceptive fibers inhibits the firing of nociceptive fibers in the laminae in the dorsal horn.

The application of the pyramidal thorn patches only makes patients forget the pain. It is by no means a complete recovery for the cause of the pain. In the case of chronic pain, however, the cause of the pain is often unknown, and in that sense, just to make patients forget the pain is very important. On the other hand, the body may use its own restorative powers to remove the cause of the pain, while the pain is forgotten. In any case, the patch application does not directly cure the cause of the pain.

Using NIRS, Miyashiro et al. investigated the brain regions, especially the DLPFC, associated with pain during patch treatment [21]. NIRS is considered suitable for studies of pain-induced changes in brain [28]. Oxyhemoglobin levels recorded with NIRS were likely to be decreased in the left DLPFC on the basis of NIRS measurements during patch treatment, suggesting that the left DLPFC is involved in pain relief (Figure 2). The findings suggested that the left DLPFC is a candidate target brain region for pain therapy. That is, even if the detailed cellular/molecular mechanisms of this type of pain relief are unknown, it is important to determine what types of stimuli can decrease the activity of the left DLPFC in patients with chronic pain. Finding these types of stimuli is one of ultimate goals for analgesia.

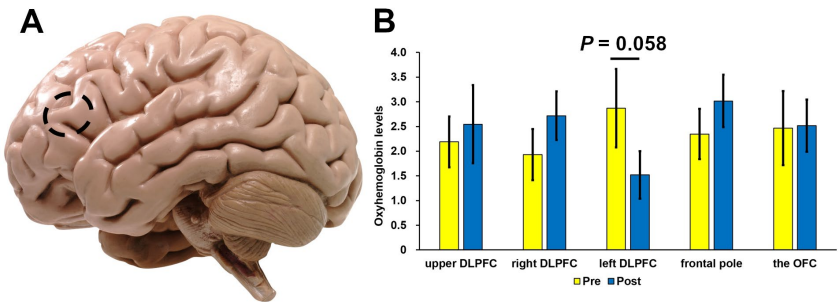

Figure 2 The dorsolateral prefrontal cortex (DLPFC). (A) Schematic representation of the left DLPFC as indicated by the dashed circle. (B) Changes in oxyhemoglobin levels normalized with the Z-score before (Pre) and after (Post) patch treatment in patients with pain. In the left DLPFC, oxyhemoglobin levels tended to be reduced during patch treatment (Wilcoxon signed-rank test, $P = 0.058$). This reduction was supported by the correlation coefficient ($r = 0.68$) calculated for the left DLPFC activity between before patch treatment (i.e., Pre) and after patch treatment (i.e., Post). Reprinted from [21] under a CC BY license.

Mindfulness for Pain Relief: fMRI Study

Mindfulness is defined as the awareness that emerges when attending nonjudgmentally to a purpose in the present moment as the experience unfolds moment by moment [29,30]. A basic breath-focused sitting mindfulness meditation is as follows [31]: Settle into a comfortable sitting posture. (Here we should note that the participants in the mindfulness protocol sit in a straight-backed chair or sit cross-legged on the floor. That is, the mindfulness protocol does not use the supine position. It is important to avoid the effects of position on the autonomic nervous system, as described above.) Anchor your attention on the movement of your breath. Be aware as the breath enters the body, leaves the body, and of the pauses in between. Inevitably the mind will at times wander from the breath, and the moment of awareness that the mind has wandered and is no longer on the breath is mindfulness itself. Simply notice when a thought, emotion, or sensation arises and calls for attention, acknowledge it, and nonjudgmentally label it – 'thinking' or 'sadness' – and then, with kindness and gentleness, usher the attention back to resuming awareness of the movements of the breath. Each time the mind wanders, this same, compassionate response and curious attention are applied. The breath is harnessed as an anchor to the present moment, always available to attend to.

In the last several decades, enhanced mindfulness has been incorporated into therapeutic approaches, including treatments for people with chronic pain [32,33]. Many previous studies have provided evidence supporting the efficacy of mindfulness-based stress reduction for the treatment of chronic pain [34–36]. When people with chronic pain can uncouple their response to pain from the actual physical sensations, they can form a healthier response and suffer less.

In many cases, the brain activity associated with the pain relief by mindfulness meditation has been examined with fMRI. Various brain regions that are activated or inactivated during pain relief have been reported by various researchers. Gard and colleagues showed that activation of the lateral prefrontal cortex was decreased, whereas activation of the right posterior insula was increased when mindfulness reduced the pain of unpleasant electric stimuli [37]. Seminowicz et al. reported that when a headache pain intensity was reduced by mindfulness-based stress reduction, the fMRI data showed activation of the left DLPFC and the cognitive task network [38].

Zeidan and colleagues paid special attention to the differences between the effects of mindfulness meditation and those of placebo analgesia using fMRI [39]. Their results revealed that mindfulness meditation reduces pain intensity and pain unpleasantness ratings more than placebo analgesia. The pain relief experienced due to mindfulness meditation is associated with greater activation in the orbitofrontal, subgenual anterior cingulate, and anterior insular cortex. Placebo analgesia is associated with activation of the DLPFC and inactivation of the secondary somatosensory cortex. These findings indicate that, from the viewpoint of brain regions, the change observed in the DLPFC by patch treatment bears some resemblance to placebo analgesia, even though the activation/inactivation of the DLPFC is opposite in these 2 treatments.

For this complicated conflict, we should consider the following points. One meta-analysis article showed that there was low-quality evidence that mindfulness meditation was associated with a small decrease in pain, compared with all types of controls, whereas significant effects were found for 'depression symptoms and quality of life' [40]. This issue may be explained by the fact that chronic pain is frequently accompanied by psychiatric disorders such as pain medication addiction and depression that make treatment complicated. The influence of long-term mindfulness practice has been examined on pain and pain anticipation [41]. Mindfulness meditation-related pain reduction was associated with increased cognitive and emotional control produced by cultivating an attitude of acceptance toward impending stimuli. During pain, meditators exhibited greater activation in brain areas responsible for encoding sensory aspects of noxious stimulation. At the same time, brain inactivation was observed for meditators in regions involved in emotion, memory and appraisal, accompanied by the lowest pain ratings. These results were interpreted as reflecting a mental state wherein the meditators were fully attentive to the sensory properties of the stimuli but simultaneously inhibiting appraisal, elaboration, and emotional reactivity

Effects of Oxytocin on Pain Relief

Oxytocin is a peptide hormone comprising 9 amino acids that is synthesized in neurons of the supraoptic nucleus and paraventricular nucleus of the hypothalamus after specific stimulation of the brain [42]. These neurons project to the posterior pituitary, where oxytocin is released into the blood for delivery to peripheral tissues as well as into the brain [43,44]. The effect of oxytocin on pain relief should be considered [16,45,46], because of its antinociceptive effects [47–49]. We hypothesized that oxytocin secretion is increased during pain relief [16], but the molecular and cellular mechanisms of pain relief by oxytocin have not yet been established because of its complicated effects [49].

The impact of oxytocin on DLPFC function seems great. For example, oxytocin significantly attenuated the aberrant alpha activity in the left DLPFC, which is thought to be involved in working memory and cognitive control, in trauma-exposed war veterans [50]. Furthermore, oxytocin is known to affect the effective connectivity between DLPFC and the other brain regions. Individuals with posttraumatic stress disorder (PTSD) by application of nasal spray of oxytocin

performed better in the 2-back task and their connectivity between DLPFC and anterior cingulate increased in the 2-back task, compared with individuals with PTSD on placebo [51]. Anterior cingulate is involved in various functions, such as attention allocation, reward anticipation, decision-making, ethics and morality, impulse control and emotion. When the potential interaction between an oxytocin receptor single-nucleotide polymorphism (rs2268493) and material care on patterns of effective connectivity was investigated during explicit emotion processing, subjects carrying this rs2268493 T allele and reporting low maternal care had different patterns of amygdala-DLPFC effective connectivity, compared to the other genotype/maternal care groups [52]. Oxytocin modulates the effective connectivity between the precuneus and left DLPFC, controlling social cognition [53]. The precuneus is involved in self-centered mental imagery strategies and subserving successful episodic memory retrieval. On the other hand, in the human postmortem brain tissues of the patients of depressive or bipolar disorders, significantly increased oxytocin receptor mRNA levels were observed in DLPFC [54]. Indeed, the relationship between the function of oxytocin in DLPFC and the pain relief has not yet been clarified, but in the near future oxytocin will become a key factor in the DLPFC about the pain relief.

In the central nervous system, oxytocinergic antinociception is thought to be mediated by GABAergic interneurons that inhibit the primary nociceptive inputs conveyed by Aδ and C fibers to the spinal cord [55,56]. The involvement of GABA mediated by oxytocin in pain relief was also confirmed in newborn rats [57]. Furthermore, the involvement of vasopressin receptors was found using knock-out mice, because oxytocin receptor knock-out mice displayed a pain phenotype identical to wild-type mice, whereas oxytocin-induced analgesia was completely absent in vasopressin-1A receptor knock-out mice [58]. The complicated effects of oxytocin may result from the dual role of oxytocin receptors on neural excitability. At low oxytocin concentrations, oxytocin receptors activate Gq/phospholipase C and induce intracellular Ca^{2+} release, thereby inhibiting the inward rectifying K^{+} conductance. On the other hand, at high oxytocin concentrations, oxytocin receptors activate the inward rectifying currents via coupling to Gi and Go [59,60].

As described above, the previous studies showed that oxytocin-induced analgesia was not observed in vasopressin-receptor knock-out mice [58]. This issue is so difficult for us to explain appropriately. One speculation is as follows [for example, see 61,62]: The structurers of vasopressin and oxytocin are similar. The N-terminal six amino acid residues of these peptides are flanked by 2 cysteine residues forming an intramolecular ring. Furthermore, the signal transduction pathways activated by both vasopressin-1A receptor and oxytocin receptor are similar. These receptors couple to Gq and phospholipase C. That is, we feel compelled to consider that there is a crosstalk between the vasopressinergic system and the oxytocinergic system in response to oxytocin.

Oxytocin is rapidly metabolized; e.g., previous studies showed that the half-life of oxytocin in the blood and cerebrospinal fluid is 5 min and 20 min, respectively [63,64]. Thus, the development of a new, long-effective agonist for oxytocin receptors is anticipated [65].

Other Topics for Pain Relief

Some interesting trials were recently performed to study the mechanisms of pain relief in vitro using ‘human’ skin and neurons. Human epidermal keratinocytes and dermal fibroblasts can be easily obtained as commercially available cells, whereas human neurons are difficult to collect. Oka and Ito have attempted to prepare neurons by differentiating human dental pulp stem cells (hDPSC) [66,67] for this purpose. In particular, Arimura and colleagues compared neurons originating from hDPSCs and rat neurons isolated from the dorsal root ganglion (DRG) [67]. These 2 different types of neurons responded to some of the same neurotransmitters. Furthermore, both neuron types produced Ca^{2+} responses to activators of transient receptor potential (TRP) channels, such as capsaicin (an activator of TRPV1 channels) and allyl isothiocyanate (AITC; an activator of TRPA1 channels) [68]. Because TRP channels play a key role in pain detection [69], this finding raises hope that the neuron-differentiated hDPSCs can be used in a pain detection network as a human peripheral pain model system.

Previous studies, including Miyashiro’s studies [21], suggested that the DLPFC, especially the left side, plays a key role in pain relief. A contrary suggestion has been proposed as follows: the left DLPFC might be ‘activated’ before patch treatment because the patients ‘expect’ the pain relief. The placebo effect is considered to be due to patient expectation [70,71]. In other words, the left DLPFC may be activated before pain relief. We should note, however, that the phenomenon observed for pain relief by the patch treatment is not a placebo effect. This was demonstrated by the application of a sham patch without a pyramidal thorn to a region of pain, in which the degree of pain relief was significantly smaller than that following the application of the pyramidal thorn patch [18]. Even so, we cannot deny the possibility that the left DLPFC is activated before patch treatment because the participants might expect the patch treatment to provide pain relief. This possibility will be carefully evaluated in future studies.

Conclusions

Previous studies by Miyashiro and colleagues showed that application of pyramidal thorn patches to pain regions

decreased the degree of pain, leading to a lower oxyhemoglobin level in the left DLPFC [21]. That is, the left DLPFC is involved in pain relief. The involvement of DLPFC in pain is well known [72–74]. There was a neuroimage-based systematic review of fMRI and electroencephalography (EEG) studies assessing brain regions recruited through cognitive strategies for pain modulation [75]. The results indicated that the activation was increased in the prefrontal cortex, including DLPFC, in chronic pain population following the cognitive and meditative therapies. Seminowicz and Moayedi described that "the structure and function of the DLPFC is abnormal in some chronic pain conditions. Upon successful resolution of pain, these abnormalities are reversed" [76]. Ihara et al. suggested that the alterations of DLPFC connectivity are involved in the pathology of chronic neck pain [77]. Together, these findings suggest that more attention should be paid to evaluating the specific stimuli that activate/inactivate the DLPFC. Artificial modifications other than pharmacologic treatment of the DLPFC are strongly considered important for the control of chronic pain, eliminating the side effects of medicines and reducing medical expenses.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Author Contributions

E.I. wrote the original draft. K.O. and F.K. edited the manuscript. All the authors agreed the final version of this manuscript to publish.

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