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NEUROPHYSIOLOGY OF PLACEBO ANALGESIA: A LITERATURE REVIEW

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Abstract: Goal: Explain the neurophysiology of placebo analgesia and its clinical implications in improving the prognosis of patients with chronic pain. Method: Bibliographic review carried out in October and November 2022, through research using the keywords "placebo analgesia", "mechanisms", "pain" and "placebo effect", in the PubMed Central (PMC) database. 1448 articles were found, of which 13 were considered eligible, after being selected according to the inclusion criteria, to compose this work. Review: Several neurophysiological mechanisms of placebo analgesia were found, and despite the different effects, several brain areas are related to these mechanisms such as somatomotor networks, thalamus, insula, limbic associations and thalamic nuclei, which are mediated by important neurotransmitters. **Final considerations**: The influence of pain modulation by the subjective pain mechanism is explained, showing placebo analgesia as an important component in the prognosis of patients with chronic pain.
Keywords: Placebo analgesia; Mechanisms; Pain; placebo effect.

INTRODUCTION

The placebo effect occurs when a treatment/inert substance produces a positive psychological/physiological effect, improving the patient's symptoms, although theoretically they do not have the capacity for such action (WAI-LAN YEUNG V. et al., 2020). Recent studies reveal, in patients with pain, that the placebo effect is similar to the effects of pharmacological opioid analgesics, with such findings confirmed by meta-analysis in patients under painful stimulation. The mechanisms of effects are similar since both placebo analgesia and pharmacological analgesics increase the density of ROMs (endogenous μ-opioid receptors) in areas

responsible for pain modulation (ATLAS LY, 2021).

Pain is a subjective and conscious experience, integrated with the individual's sensory and emotional processing and context. In humans, pain is at the center of multiple health crises, as is the case with chronic pain, and chronic pain is highly comorbid with other diseases. In addition, another fact that demonstrates the prevalence of pain is that more than 11% of American adults report experiencing daily pain (ATLAS L.Y., 2021). However, the experience of pain is not a veridical representation of tissue damage, or even a direct mapping of ascending nociceptive input to the brain, rather, pain is a fluid representation in which it is shaped by anticipated outcomes and based on contextual information. Based on this assumption, due to the activation of pain control mechanisms being frequently altered by the placebo effect, as well as the neural systems that induce and modulate pain being well defined, pain ends up serving as a good study model for placebo analgesia (SCHAFER S.M. et al., 2018).

In recent years, much has been studied about placebo analgesia and its results for chronic pain in adult patients. Its effects have been widely used in several areas of health, including medicine (ATLAS L.Y., 2021). Recent studies have shown that not only consumption, but the simple association with a placebo analgesic is capable of affecting pain assimilation in an adult (WAI-LAN YEUNG V. et al., 2020). However, although placebo analgesics are widely known to alleviate various manifestations of clinical conditions, the understanding of their mechanisms and how their interactions are able to generate relief in chronic pain is still poorly understood (SCHAFER S. M. et al., 2018).

In this sense, evaluating the physiological mechanisms involved in placebo analgesia, and how knowledge about them can help in the management of patients with different clinical conditions of chronic pain, may contribute to a better understanding of the effects of such substances, how to apply them and on whom to use them. Through the theoretical basis provided by the current scientific literature, this bibliographic review aims to understand and explain the neurophysiology of placebo analgesia and its clinical implications in improving the prognosis of patients with chronic pain.

METHODOLOGY

This is a bibliographic review developed in October and November 2022. The research was developed through the following guiding question: "What are the physiological mechanisms involved in placebo analgesia and how knowledge about them can help in the management of patients? with different chronic pain conditions?". Searches were performed in the PubMed Central (PMC) database. The descriptors were used in combination with Boolean terms AND and OR through the following string: "((placebo analgesia) OR ((pain) AND (placebo Effect))) AND (mechanisms)". Without application of search filters, 1448 articles were found from the search indicated above. Applying the 5-year filter, 357 articles were found, so the inclusion criteria were: English and German languages; publication interval of 5 years (from 2018 to 2022) and that addressed themes proposed by this research; meta-analysis studies, systematic review, narrative review or randomized controlled clinical study. Exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and which did not meet the other inclusion criteria. Thirteen articles were selected from the database (PubMed Central) to compose the collection.

REVIEW

In recent years, research into the neurophysiological basis of placebo analgesia has been intense and several biochemical and psychological mechanisms have been discovered. By definition, it is known that the placebo effect occurs when changes in pain perception occur that exceed the specific effect of analgesic therapy, whether pharmacological, psychological or physical (RHUDY J.L. et. al., 2018). Numerous studies have shown that treatment expectations are a decisive factor in therapeutic success (ASAN L. et al., 2022). However, the effects vary from study to study, as well as the related brain mechanisms. According to Tu Y. et al. (2021), placebo analgesia and nocebo hyperalgesia specifically start from the dorsal lateral prefrontal cortex and then trigger the descending pain modulator system of the brain and other pain regulation pathways (TU Y. et al., 2021).

Some studies indicate a significant response in pain reduction or control, at the level of the right insula and cerebellum; coupled with decreased neuronal activity in the bilateral supplementary motor area and middle cingulate cortex. In studies related to network and region, positive associations were found with most thalamic nuclei, nuclei related by nociception pathways and also limbic association. Regarding negative associations, activity is found in the lateral, medial and pulvinar geniculate nuclei, which play roles related to vision and hearing, and which in turn have pathways that pass through such structures. Negative relationships correlated with placebo analgesia have also been reported for the thalamus, anterior insula, secondary somatosensory cortex and basal ganglia (ZUNHAMMER M. et al., 2022).

In line with these findings, according to magnetic resonance-based studies, the decrease in pain perception associated with placebo and its correlation with pain indices, especially with regard to the behavioral factor, were more prominent in regions located within the area related to pain. ventral region and somatomotor cortical networks, including the anterior insula and targets of the spinothalamic tract, as well as the anterior posterolateral thalamic nuclei (VPL), the posterior insula and, in addition, the habenula (ZUNHAMMER M. et. al., 2021). Similarly, experimental analyzes with functional neuroimaging have shown that the effect of placebo analgesia is mediated by important neurotransmitters including endogenous opioids and dopamine (ASAN L. et al., 2022).

On the other hand, according to the meta-analysis by Colloca L. (2020), despite the involvement of thalamo-cortical connections related to nociception and pain, placebo treatments affect pain through brain mechanisms largely independent of the effects on nociceptive processing of "bottom up". Such findings explain the difficulty of several studies in making an objective evaluation of the effects of such treatment on the neurophysiology associated with pain, due to the fact that patients also evaluate their pain within a complex set of personal and cultural factors, such as expectations, beliefs, associative learning and social cognition. Such factors lead to disagreements for clinical trials that do not take into account the multidimensional experience of pain (ZUNHAMMER M. et al., 2018). Added to this, its neurobiological effect is linked not only to processing but also to early coping in pain control (ZUNHAMMER M. et al., 2022).

According to Zunhammer M. et al, 2022, one of the mechanisms of placebo treatment is the effect that it can cause in various areas of the brain, not only those involved in nociceptive stimuli, with regard to pain. This effect may, consequently, alter nociception or possibly

cognitive processes that are related to feelings or decisions in the face of pain. Based on this premise, it is emphasized that the placebo effect has a wide range of mechanisms, whether they are reducing pain, or, in relation to what was mentioned above, modifying the intensity or even the behavior in relation to the painful manifestation and, consequently, altering its perception per se. Colloca L. (2019), points out that placebo effects are mostly responsible for the effectiveness of non-pharmacological treatments, such as homeopathy.

It is noteworthy that most studies and analyzes seek to focus on showing whether placebo analgesia can lead to changes in the Neurological signature of pain, as well as analyzing how the mechanisms of placebo treatment can potentially strongly affect not only nociception. and but definitely the generation of pain (ZUNHAMMER M. et al., 2022). In addition, expectations regarding the beneficial effects of the treatment can facilitate the treatment and also lead to a decrease in nociception processes at the level of the initial subcortical areas and the spinal cord, generating a behavioral change when experiencing pain (COLLOCA L., 2020).

Several studies have demonstrated an expressive and sustained difference between drug and placebo in the primary outcome of pain manifestations (KLINGER R. et al., 2018). According to Chengyong L. et al. (2020) it is still unclear whether placebo treatments affect patients with chronic pain. Placebo analgesia, in most studies, is reproducible in healthy subjects, and placebo responses tend to exhibit particular cognitive traits such as higher levels of dispositional optimism and reduced levels of state anxiety. Patients with chronic pain have psychological comorbidities such as anxiety, depression, pain catastrophizing and cognitive impairments. Because of this, several studies examining the role of expectation and anxiety in placebo pain modulation found a reduction in placebo analgesia in patients with chronic pain when compared to healthy individuals (POWER A. et al., 2020). Although the placebo response is generally high in pain studies, there are genetic, psychological and biological factors of patients that need to be considered since they can affect their response, in addition to the fact that placebo effects involve endogenous systems, that is, their effects also depend on these systems and which disease it is about (VASE L.; WARTOLOWSKA K., 2019). However, Colloca L.(2020), states that it can change the perception of pain, leading to repercussions on the body's own endogenous pain modulator system, in the face of pain disorders, especially in cases of chronic pain. Colloca L. (2020) further states that the relevance given to treatment can help trigger significant positive clinical effects.

FINAL CONSIDERATIONS

It is known that the placebo effect is an efficient therapeutic mechanism to confront, strengthen and/or refute the effectiveness of point 1: certain treatments. In this sense, we sought to understand more clearly the neurophysiology of placebo analgesia and its clinical implications in improving the prognosis of patients with chronic pain. With this objective in mind, the influence of pain modulation by the subjective pain mechanism is explained, showing placebo analgesia as an important component in the prognosis of patients with chronic pain. Be it for its influence in changing the perception of pain as well as for the consequent improvement in the quality of life of individuals. However, although it is a topic of great relevance, the exact mechanisms of the neural pathways, signaled by the administration of placebo analgesia, are still poorly understood, thus requiring

research with randomized studies, with the follow-up of patients undergoing treatment for chronic pain responsive or not to placebo analgesia. Thus, the management of patients with illnesses characterized by chronic pain can benefit from a more assertive direction in order to minimize the implications of the side effects of conventional pharmacological therapy.

REFERENCES

ASAN, Livia et al. Neurobiologische und neurochemische Mechanismen der Placeboanalgesie. **Schmerz**, v. 36, p. 205-212, 2022.

ATLAS, Lauren Y. A social affective neuroscience lens on placebo analgesia. **Trends in Cognitive Sciences**, v. 25, n. 11, p. 992-1005, 2021.

COLLOCA, Luana. Placebo effects in pain. **Elsevier**, v. 153, p. 167-185, 2020.

COLLOCA, Luana. The placebo effect in pain therapies. **Annual review of pharmacology and toxicology**, v. 59, p. 191, 2019.

KLINGER, Regine et al. Clinical Use of Placebo Effects in Patients With Pain Disorders. **Int Rev Neurobiol,** v. 139, p. 107-128, 2018.

POWER, Andrea et al. Individuals with chronic pain have the same response to placebo analgesia as healthy controls in terms of magnitude and reproducibility. **Pain**, v. 161, n. 12, p. 2720-2730, 2020.

RHUDY, Jamie L. et al. The influence of placebo analgesia manipulations on pain report, the nociceptive flexion reflex, and autonomic responses to pain. **The Journal of Pain**, v. 19, n. 11, p. 1257-1274, 2018.

SCHAFER, Scott M.; GEUTER, Stephan; WAGER, Tor D. Mechanisms of placebo analgesia: a dual-process model informed by insights from cross-species comparisons. **Progress in neurobiology**, v. 160, p. 101-122, 2018.

TU, Yiheng et al. Manipulating placebo analgesia and nocebo hyperalgesia by changing brain excitability. **Proceedings of the National Academy of Sciences**, v. 118, n. 19, p. e2101273118, 2021.

VASE, Lene; WARTOLOWSKA, Karolina. Pain, placebo, and test of treatment efficacy: a narrative review. **British journal of anaesthesia**, v. 123, n. 2, p. e254-e262, 2019.

WAI-LAN YEUNG, Victoria; GEERS, Andrew L.; COLLOCA, Luana. Merely possessing a placebo analgesic improves analgesia similar to using the placebo analgesic. **Annals of Behavioral Medicine**, v. 54, n. 9, p. 637-652, 2020.

ZUNHAMMER, Matthias et al. Meta-analysis of neural systems underlying placebo analgesia from individual participant fMRI data. **Nature communications**, v. 12, n. 1, p. 1-11, 2021.

ZUNHAMMER, Matthias et al. Placebo Effects on the Neurologic Pain Signature. **JAMA Neurology,** v. 75, n. 11, p. 1321-1330, 2018.