P.2.b.012 The role of the noradrenergic system in the affective sphere of chronic neuropathic pain

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Chronic pain is a complex experience comprising two different components: sensorial and affective components of pain. Chronic pain can become maladaptive and incapacitating leading to a worsening in the prognosis, the response to treatment and reducing life quality of patients. Furthermore, many psychobiological factors get worse the affective component of pain leading to depressive symptoms. However, little is known about the possible modifications of pain processing when chronic pain condition manifests symptoms of depression. Noradrenergic system is a pivotal candidate projecting descending and ascending regulating sensorial and emotional aspects of pain, respectively. In the present study, we assessed the role of noradrenergic system in the sensorial and emotional components of pain in rats submitted to chronic pain and/or depression.

Chronic constriction injury (CCI) [1] was used as a model of chronic neuropathic pain and chronic mild stress (CMS) [2] as a model of depression, generating four experimental groups: Sham-control, Sham-CMS, CCI-control and CCI-CMS. Parallel, in order to study the involvement of noradrenergic system in the sensorial and affective components of pain, DSP-4 (50 mg/kg), a neurotoxin which selectively damages noradrenergic projections and desipramine (DMI, 10 mg/kg), a noradrenaline reuptake inhibitor, were administered intraperitoneally to CCI-control and CCI-CMS groups the same day of CCI and CMS induction. After 14 days of treatment, sensorial and affective components of pain were evaluated by using nociceptive tests (von Frey and acetone test) as well as the place escape avoidance test (PEAT) [3], respectively. Additionally, we evaluated anhedonia in all experimental groups. All results were analyzed using two-way analysis of variance (ANOVA) with or without repeated measures, as appropriate. The results revealed that the group with chronic pain and depression (CCI-CMS) showed the most negative pain experience in the PEAT followed by the group with chronic pain (CCI-control). However, DMI administration prevented the worsening of affective component of pain experimented by CCI-control and CCI-CMS groups. Interestingly, DSP-4 administration enhancement the negative pain experience in CCI-control group showing similar score that CCI-CMS in the PEAT. Regarding to the sensory component of pain, both CCI-control and CCI-CMS groups showing similar degree of mechanical allodynia in the von Frey test. DMI administration prevented the development of allodynia while DSP-4 did not show significant changes in nociceptive threshold. On the other hand, both Sham-CMS and CCI-CMS development anhedonia after 14 days of CMS and DMI prevented it. Interestingly, DSP-4 administration induced anhedonia in CCI-control and enhancement anhedonia in CCI-CMS group.

In conclusion, depression highly determines affective-pain experience and the inhibition of noradrenaline reuptake prevents it. On the other hand, the destruction of noradrenergic system, by DSP-4 administration, enhancement the negative pain experience leading to a concomitant state of chronic pain and depression. Overall suggests that noradrenergic system play a major role regulating the affective-interpretative pain experience.

References

[1] Bennett G.J, Xie Y.K., 1988. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 33: 87–107.
[2] Willner P., 2005. Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effects of CMS. Neuropsychobiology 52: 90–110.
[3] LaBuda C.J., Fuchs P.N., 2000. A behavioral test paradigm to measure the aversive quality of inflammatory and neuropathic pain in rats. Exp Neurol 163: 490–4.

P.2.b.013 Does the early response to deep brain stimulation in depression represent a placebo or electrode insertion effect?

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Background: Affective disorders and particularly Major Depression Disorder (MDD), are among the most severely disabling disorders in the world. Despite the treatments available, between 30 and 40% of the patients fail to respond to first-line treatments and between 5% and 10% fail to respond to more aggressive treatments. Deep brain stimulation (DBS) in the subgenual cingute (Cg25) is a new and promising non-pharmacological therapeutic alternative for the management of severe and resistant MDD; although the precise mechanisms underlying its therapeutic effects have not yet been elucidated. Interestingly, initial clinical studies have reported a significant early improvement in patients, followed by a decline within the first month of treatment. However, this unexpected phenomenon, attributed to a potential placebo effect or a physiological response to probe insertion, remains poorly understood.

Methods: To address this question, we focused on the early phase of DBS therapy directed towards the Cg25 in a controlled clinical trial of patients diagnosed with treatment-resistant MDD. In addition we characterized in experimental animals (which are devoid of any placebo effect), the effect of electrode implantation using the forced swimming test (FST). Furthermore, we also study the neurophysiological changes focusing on modifications to the ventral part of the medial prefrontal cortex, mPFC (rodent SCG correlate). In addition, we evaluate the effect of antinflammatory and analgesics drugs in this issue. Results were analyzed by a one or two-way ANOVA followed by Bonferroni test. $p < 0.05$ were considered to be significant.

Results: We found an antidepressant-like effect in the FST in rats implanted with electrodes (irrespective of whether they received electrical brain stimulation), which was not related with a general increase in locomotor activity. This effect was temporally correlated glial fibrillary acidic protein (GFAP) immunoreactivity and was prevented by a treatment with antiinflammory