**TREATMENT CANNABIDIOL IN PRE-CLINICAL MODEL OF NEUROPATHIC PAIN: MODULATION OF AFFECTIVE-MOTIVATIONAL BEHAVIOR AND REDUCTION OF CHRONIC NEURONAL ACTIVITY OF CORTICOLIMBIC CIRCUIT.**

Gleice Kelli Silva-Cardoso1,3, Willian Lazarini-Lopes2,3, Antônio Zuardi2,3, José A. Crippa2,3, Jaime Hallak2,3, Norberto Garcia-Cairrasco2,3 and Christie Leite-Panissi1,3

1Laboratory of Pain and Behavior Neurophysiology, Department of Psychology, Faculty of Philosophy, Sciences and Letters of Ribeirão Preto, University of São Paulo, São Paulo, Brazil. E-mail: gleicekelliribeiro@gmail.com

2Department of Neurosciences and Behavioral Sciences, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil.

3National Institute of Science and Technology - Translational Medicine (INCT-TM; FAPESP / CNPq), São Paulo, Brazil

Introduction: In the general population, the incidence of chronic pain is 6% to 8%, and its impact on quality of life, mood, and sleep exceeds the burden of its causes pathology. In this perspective, cannabidiol (CBD) is considered a promising strategy for treating neuropathic pain. Our objective was to evaluate the possible modulation of the effect of CBD on receptors CB1, TRPV1, and Fos-B protein expression, using systemic treatment with CBD (3 days) in rats submitted to sciatic nerve constriction (CCI), nociceptive tests (TN), open field (OF), rotarod and place preference - pain aversion paradigm (CPPA).

Methods: 80 Wistar rats (220 g) were used (CEUA-USP: 208.1.103.58.5). The rats were submitted to TN and rotarod, followed by surgical procedure (CCI or sham-operated, SHAM) on day zero, and the development of neuropathy was followed for three weeks by TN (i-von Frey, hot plate ii and iii -acetone). The CPPA baseline was performed between days 15 and 18 after the injury, along with the rotarod test. Lidocaine (i.m. injured paw) was used as a positive and paired control in the context of a longer baseline stay. CBD (i.p.) was matched in the least preferred context at baseline. In both conditions, saline solution was applied to the popliteal fossa of the injured paw 10 min before CPPA. On day 24, rats were submitted to OF 4 hours after drug application. After 24 hours, the rats were exposed to CPPA without drug application. Immunofluorescence for CB1 and TRPV1 receptors in the insular cortex (IC), anterior cingulate cortex (ACC), basolateral amygdala (BLA), and dorsal (HD) and ventral (VH) hippocampus regions. Further, immunohistochemistry was performed to label Fos-B protein, ACC, BLA, and CA1 from the DH. The two-factor ANOVA test was used, followed by the Tukey test, P < 0.05.

Results: Treatment with CBD for three days at different doses (0.3, 3, and 10 mg/kg i.p.) showed an anti-allodynic effect (P < 0.05) in CCI rats (i, ii and iii, P < 0.05) In the OF, CBD showed an anxiolytic effect (P = 0.0008) in CCI animals. CB1 receptor expression: ACC, IC, BLA, DH e VH; condition factor (SHAM or CCI, P< 0.05) and treatment factor (Vehicle or CBD, P < 0.05). Expression of TRPV1 receptors: ACC, IC, BLA, DH, and VH; condition factor (SHAM or CCI, P < 0.05) and treatment factor (Vehicle or CBD, P < 0.05). On the expression of Fos B, ACC condition factor and treatment factor (P < 0.05); BLA condition factor and treatment factor (P < 0.05).

Conclusion: In the analyses, treatment with CBD 3 mg/kg showed increased expression of the receptor CB1 and TRPV1 in the regions studied, this synergistic effect offers favorable perspectives for new pharmacological approaches in the treatment of neuropathic pain, and we infer that these receptors can modulate this effect. Furthermore, treatment with CBD 3 mg/kg could reverse the chronic marking of neuronal activation in both ACC and BLA. This effect may explain CBD modulation effects on emotional modulation areas of chronic pain.

Financial support: FAPESP (2018/06877-5); INCT - National Institute of Science and Technology - Translational Medicine (CNPq nº 465458/2014-9; FAPESP nº 2014/50891-1), CAPES-PROEX (001), CNPq.