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## TÍTULO

LIMONENE MODULATES THE HYPERALGESIA AND DEPRESSIVE-LIKE BEHAVIOUR THROUGH IL-1B AND NFKB REGULATION IN MICE

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## **RESUMO**

Introduction: Interleukin 1-β is a proinflammatory cytokine involved in chronic pain process. In neuropathic pain models, evidences have suggested IL-1β activates astrocytes and microglia which may change pain behavior and related mechanisms. Previous study from our group with limonene has demonstrated its antihyperalgesic and antidepressive actions in neuropathic pain model. Objectives: The present work has investigated the antihyperalgesic and antidepressive effects of (R)-(+)-llimonene against IL-1β administered intrathecally. Material and Methods: Male Swiss mice (n=6) received IL-1β (1000pcg) or sterile saline as control intrathecally. One hour before injections animals were treated orally with limonene (10mg/kg) or saline solution as a control. Mechanical sensitivity was measured with an electronic Von Frey apparatus and cold sensitivity with acetone test after 2 and 3 hours of the injections. To evaluate depression, tail suspension test was performed after 4 hours of the injection. To assess NFkB levels, dorsal spinal cord was collected and western blot analysis conducted. Results: After the intrathecal administration, IL-1 $\beta$  was capable to decrease mechanical and cold hypersensitivity in mice when compared to control. It was not observed any significant changes in immobility between the treated groups and control. Limonene significantly increased mechanical sensitivity after 3 hours of the injection with maximum inhibition (Imax) of 81±3% when compared to the control group. Increased cold sensitivity was also observed after 2 and 3 hours of the injection with Imax of 81±4% after 2 hours when compared with control group. Western blot assay demonstrated Limonene was capable to significantly decrease the expression of NFkB protein in the spinal cord. Discussion and Conclusion: All results of the present work show that when administered intrathecally,IL-1β caused hyperalgesia but did not demonstrated depressive behavior in mice. Oral treatment with Limonene showed antihyperalgesic effects that may be related to the reduction of NFkB expression in the spinal cord.