Morphine-withdrawal induces conditioned place aversion. A study of the extinction of negative affective memory.

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Addiction is a chronic disorder characterized by compulsive drug-seeking, loss of control of consumption and relapse. Opioids, like morphine and derivatives, are substances with a great ability to induce addiction. Conditioned place aversion (CPA) has been used to assess the emotional component of opioid withdrawal [1]. These animal models mimic the behaviors of the negative affective component of the withdrawal syndrome. Extinction period of positive affective memory of drug taking and negative affective memory of drug withdrawal might be important for the clinical treatment of drug addiction.

Male swiss mice were housed 4–6/standard cage in a temperature-controlled environment, received ad libitum access to food and water and were maintained on a 12-h/12-h light/dark cycle. Mice were habituated to the testing room for at least 1 week prior to the experimental manipulations. Animals were rendered dependent on morphine by i.p. injection of increasing doses (10-60 mg/kg). This pattern of morphine administration, which involves ascending drug doses, has been used extensively to study opioid tolerance and dependence [2]. The control group received saline. Body weight gain and loss was measured. Negative state associated with naloxone-precipitated morphine withdrawal was examined by using CPA paradigm. This procedure induces place aversion when the animals relate the environment with the negative effects of morphine withdrawal syndrome. Extinction training began 24 h after the post-training CPA test.

The weight of the animals was recorded the days of morphine or saline injection since it is known that chronic morphine treatment induces a decrease in body weight gain due to a lower caloric intake. t-test analysis revealed that morphine treatment induced a significant lower body weight gain compared to saline. However, the injection of naloxone did not induce differences in the body weight loss in the morphine or saline group, although other somatic opioid withdrawal signs were observed (jumping, grooming, rearing, rubbing).

Our results also show an aversive effect of naloxone in morphine-dependent animals (-97.27±13.17) compared to the saline+naloxone group (16.07±25.64).

We examined extinction of CPA score in withdrawn mice and we observed that all our animals had extinguished their aversion 10 days after the beginning of the experiments, being days 7 and 8, the days with more animals extinguishing their aversion score.

In conclusion, our preliminary behavioral findings, together with molecular studies, may facilitate the development of treatments for opioid addiction.