High-fat diet-induced obesity increases chronic pain susceptibility: preliminary results from the mesocorticolimbic system role in mice

A. F. Brandao[1], I. J. M. Bonet[1], M. O. F. Pagliusi Junior[1], S. F. Magalhaes[1], C. R. Sartori[1]
[1]Laboratory of Pain Studies (Le*d*), Institute of Biology, Department of Structural and Functional Biology of State University of Campinas, UNICAMP.

Introduction: Chronic pain and obesity are the two most prevalent health problems in the modern world and these chronic illnesses are likely to be deeply correlated. In fact, epidemiologic data have shown that patients with obesity have an increased chronic pain susceptibility [1], and some researchers propose that this is related to the increased body weight [2]. However, another hypothesis suggests that the neuroplasticity in the mesocorticolimbic system, particularly in the dopaminergic signaling between ventral tegmental area (VTA) and nucleus accumbens (NAc) [3,4], is underlying the chronic pain susceptibility. Thus, this study investigates how high-fat diet-induced obesity can promote neuroplasticity in the mesocorticolimbic system and, as a consequence, induce mechanical chronic pain susceptibility.
Materials and Methods: Twenty (six-weeks-old) male C57BL/6JUnib mice were randomly and individually housed with *ad libitum* food and water. Mice were divided in two groups and, for eight weeks, fed with a standard chow diet (CD) (16% from fat) [5] or with a high-fat diet (HFD) (58% from fat) [6]. During all the study, weight was measured weekly. Epidydimal, mesenteric and retroperitoneal fat tissues were extracted and weighted. The inflammatory chronic pain induction was adapted from Villarreal et al., in which 18µl of prostaglandin E2 (PGE) (90 ng) or 18µl of saline (0.9% NaCl) was administrated in the plantar surface of the right hind paw for seven consecutive days. Therefore, CD and HFD groups were subdivided in four groups: CD group that received saline (CD-SAL) or PGE (CD-PGE) and, HFD group that received saline (HFD-SAL) or PGE (HFD-PGE). The mechanical nociceptive threshold was assessed using an electronic von Frey apparatus adapted for mice paw [8] and was expressed by delta threshold in grams (g). Experimental procedures were approved by CEUA-UNICAMP, nº4243-1.
Results: HFD group presented higher total body weight ($p<.05$ from the fifth week on) and fat tissue ($p<.001$) when compared to CD group. ANOVA revealed a diet*time interaction ($p=.01$) and *posthoc* analysis showed that PGE groups (HFD and CD) had higher mechanical nociception threshold 1 day after PGE administration when compared to CD-SAL ($p<.01$) but not HFD-SAL (vs HFD-PGE $p=.89$; vs CD-PGE $p=.99$). Seven and 14 days after PGE administration, only the HFD-PGE group showed a significant increase in the mechanical nociception threshold (7 days $p=.02$; 14 days $p=.01$) when compared to all other groups. Results did not alter when adjusted for total body weight.
Discussion: Mice with high-fat diet-induced obesity have increased mechanical nociception threshold, even when adjusted for total body weight, as has been recently showed [9]. The neuroinflammation already linked to high-fat diet may be promoting several alterations in the central nervous system signaling, particularly dopamine, leptin and/or inflammatory cytokines' communication within the mesocorticolimbic system.
Conclusion: High-fat diet increases the mechanical nociception threshold in mice and that is unrelated to total body weight. Future molecular approach is necessary to understand the neuroplasticity role underlying the chronic pain susceptibility promoted by the high-fat diet.

References: [1] McCarthy LH et al., J Am Geriatr Soc 57:115–9, 2009;
[2] Grotle M et al., BMC Musculoskelet Disord 9:132, 2008;
[3] Taylor AMW et al., J Neurosci 35:8442–50, 2015.
[4] Kato T et al., Neurosci Lett 629:73–8, 2016;
[5] Reeves PGG et al., J Nutr 123:1939–51, 1993;
[6] Cintra DE et al., PLoS One 7:e30571, 2012;
[7] Villarreal CF et al., Life Sci 85:822–9, 2009;
[8] Martinov T et al., J Vis Exp e51212, 2013;
[9] Song Z et al., Sci Rep 7:10350, 2017;