EVALUATION OF THE EARLY HEPATIC REGENERATION CAPACITY OF OBESE MICE WITH DELETION OF THE α7 NICOTINE CHOLINERGIC RECEPTOR (α7nAChR)

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Introdução: Hepatic steatosis is the hallmark of non-alcoholic fatty liver disease (NAFLD) due to obesity, which can progress to more critical and irreversible stage, such as non-alcoholic steatohepatitis (NASH), cellular cirrhosis and hepatocarcinoma (HCC). In advanced cases of the disease, Partial Hepatectomy (PHx), which consists of resection of the dysfunctional part of the liver, may be recommended due to the maintenance of a healthy tissue. The healthy hepatic remaining will be responsible for regenerating the organ, restoring its mass and primitive function. During liver regeneration an essential inflammatory process occur to activate a variety of signaling pathways to induce the expression of genes involved in cell growth and differentiation. Recent studies proposed that the cholinergic anti-inflammatory pathway can attenuate inflammatory response in critical situations that occur in various organs, including liver, through JAK2/STAT3 signaling pathway activated by a receptor called alpha7 nicotinic cholinergic (α7nAChR). Recent studies from the “Laboratory of Metabolic Disorders (LabDiMe)”, have shown that offspring of obese dams have impaired regeneration capacity, however, in this study, the role of the cholinergic anti-inflammatory pathway against the inflammatory process resulting from the consumption of a hypercaloric diet was not evaluated. Little is known about the influence the α7nAChR receptor during liver regeneration after PHx in animals with diet-induced obesity. Therefore, investigations are needed about the role of the α7nAChR receptor in the regulation of the liver regenerative process, to understand the participation in the hepatic regenerative capacity, induced by mechanical insult, and eventually in the potential of therapeutic targets that can be modulated by dietary and/or pharmacological intervention to promote adequate organ regeneration. **Objective:** to evaluate the early regenerative capacity of α7nAChR receptor knockout and obese mice (male and female) after PHx. **Method:** The animals were placed in an animal room with a

light/dark cycle (12h/12h), the temperature of 21±1°C, and fed an *ad libitum* hypercaloric diet of 45% fat. After 70 days of life, the animals were submitted to PHx-2/3 and euthanized after 4 hours. The liver was excised and analyzed to verify initial liver regeneration (priming phase). The procedures were approved by CEUA, protocol no. 5692-1/2021. Data were analyzed by two-way ANOVA followed by post hoc Bonferroni tests, and a significance level of $p \leq 0.05$ was determined. **Results:** Male and female animals with α7nAChR receptor deletion after PHx showed an initial impairment in liver regeneration after 4 hours of surgery compared to WT, since they presented a decrease in STAT3 phosphorylation, as well as an increase of p-JNK under obesogenic conditions in males, denoting that the respective receptor is of paramount importance for the regenerative process. Conclusion: Given the metabolic disturbances due to the development of obesity, such as the production of pro-inflammatory cytokines, combined with the absence of the α7nAChR receptor, an important element of the anti-inflammatory response, will impair the proliferation of hepatocytes and eventually the progression of the regenerative process. Thus, the next steps will be to analyze the complex mechanisms and kinetics of final liver regeneration, to assess whether the α7nAChR receptor is truly of paramount importance during this process.

Keywords: Obesity; Liver Regeneration; α7nAChR receptor.