Título: EFFECTS OF CALORIC RESTRICTION ON BRAIN AGING AND COGNITIVE DECLINE: BEHAVIORAL AND BIOCHEMICAL ANALYSIS

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Resumen: Effects of caloric restriction on brain aging and cognitive decline: behavioral and biochemical analysis
Caloric restriction (CR) is defined as the reduction of caloric intake, without causing malnutrition. This intervention has been shown to be capable of slowing down the progression of age-related diseases, as well as increasing animal¿s lifespan. However, the potential benefits of CR on cognitive processes during aging have been scarcely studied. Therefore, the main objective of the present study was to determine whether administering a CR protocol could rescue age-induced cognitive impairment seen in short-term and long-term memory tasks, as well as modify the expression of different molecular parameters in the brain. In order to achieve this objective, we evaluated the differences between three groups of animals (old male Wistar rats, 24-27 months-old, fed a 30% CR diet; old, 24-27 months-old; and young control rats, 3-4 months-old, fed Ad libitum) in memory task performance as well as biochemical parameters.
Behavioral tasks: In order to test learning and memory, a Morris water maze (MWM), an odor discrimination task (ODT) and an object recognition memory task in a Y maze, were carried out. In order to evaluate whether emotional, motor or olfactory variables affected the outcome, an open field (OF), an elevated maze (EPM) and an olfactory perception test were administered.
Biochemical tasks: In order to analyze the general health status of the animals, blood plasma levels of triglycerides, cholesterol, alkaline phosphatase (ALP), calcium, glucose and hormones such as insulin, leptin,

corticosterone and insulin-like growth factor 1 (IGF-1) were evaluated. In addition, in order to quantify changes in monoaminergic transmission, levels of dopamine, noradrenaline, serotonin and their metabolites were obtained from the hippocampus, striatum and frontal cortex, and analyzed using High Performance Liquid Chromatography (HPLC). Furthermore, in order to explore changes in glutamatergic transmission, ionotropic NMDA and AMPA receptors, tyrosine hydroxylase, tryptophan hydroxylase and synaptophysin, a synaptic plasticity protein, were obtained from the same brain areas and analyzed by Western Blot (WB).
The main results of this doctoral thesis indicated that CR reduces the negative effects of aging on both short-term and long-term memory, as shown by the results obtained in the object recognition in the Y maze and in the MWM, respectively. In contrast, the outcome from the ODT indicated that animals that CR animals¿ performance did not improve in the long-term memory retention in an olfactory food-reinforced task, since abstaining can increase responsivity to food reward as well as the motivation to perform. Additionally, CR also enhanced the underlying biochemical processes, since it lessened the age-related diminution of AMPAr and monoaminergic levels in the HPC. However, no differences in SYP or NMDAr levels were found between groups, indicating that CR did not affect these proteins. Furthermore, results obtained in OF and EPM revealed that the nutritional intervention does not modify locomotion or anxiety levels any differently than the aging process itself. In general, CR animals presented a good health status with no malnutrition, as demonstrated by equal levels of ALP and leptin in CR and young animals. Additionally, no differences in plasma levels of hormones, such as corticosterone, insulin, glucose and IFG-1 were found between Ad Libitum aged animals and the CR group, which presented typical old-age levels.
In conclusion, CR can be considered to be a good intervention to slow down the age-related cognitive decline, as indicated in this doctoral thesis. However, the intervention is not effective in cognitive tasks that involve food reinforcement. In addition, the dietary intervention improved some of the biochemical parameters, or at least maintained normal old-age levels.