

## A multidisciplinary approach to study the brain injury in Diet-Induced Obesity (DIO) rats

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Obesity represents an independent risk factor for the development of cerebrovascular disease and cognitive impairment. The systemic effects, such as increased fat mass, hypertension, insulin resistance and general metabolic dysfunction, have been identified as factors that may lead to impaired cognitive function.

To clarify the possible relationships between obesity and nervous system changes, high-caloric Diet-Induced Obesity (DIO) rats 7 weeks-old, were studied after 17 weeks of hypercaloric diet compared to control rats with not fat diet (Chow) or to rats not developing obesity (DIO-resistant DR). Food consumption, fat mass content, blood pressure and blood parameters were assessed. Different behavioural tests were used to estimate cognitive performance. RT-qPCR, immunochemical and immunohistochemical analysis were performed to evaluate neuronal, glial and vascular markers.

The obese phenotype developed after 5 weeks of high fat diet exposure and body weight values remained higher in DIO rats compared to the control group and DR rats during the treatment. Systolic blood pressure, glycaemia and insulin were higher in DIO rats only after 17 weeks. No differences in values of total cholesterol and triglycerides were observed. Furthermore increase of thiobarbituric reactive substances and increase of oxidated proteins, was observed in the serum of DIO rats compared to Chow rats. The open-field test revealed, in the older DIO rats, a decrease of cumulative distance travelled and in the number of rearings and an increase of total immobility time. Older DIO rats only, showed a reduction of retention latency time in the passive avoidance test.

RT-qPCR, immunochemical and immunohistochemical analysis showed an increased expression of the glial-fibrillary acid protein in the frontal cortex and hippocampus of older DIO rats compared to age-matched Chow and DR rats. A decrease of neurofilament expression was found in the hippocampus of older DIO rats without changes in the number of neurons. A modulation in the Transient Receptor Potential (TRP) channels and synaptic components was highlighted in cerebral areas.

These results indicate that obesity in rats, in addition to the development of correlate cerebrovascular risk factors, causes brain injury characterized by astrogliosis, neurodegeneration and impaired learning and memory tasks. The identification of neurodegenerative changes in DIO rats may represent the first step to better characterize the neuronal modifications occurring in the obesity and propose pharmacological treatments or food strategies to counter them.

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### Keywords

Obesity, hypertension, brain injury, Diet-induced obesity (DIO) rats