PRO-INFLAMATORY MECHANISMS INVOLVED IN THE HYPOTHALAMIC CONTROL OF FEEDING AND THERMOGENESIS – IMPLICATIONS FOR THE PHISIOPATHOLOGY OF OBESITY, DIABETES MELLITUS AND CACHEXIA

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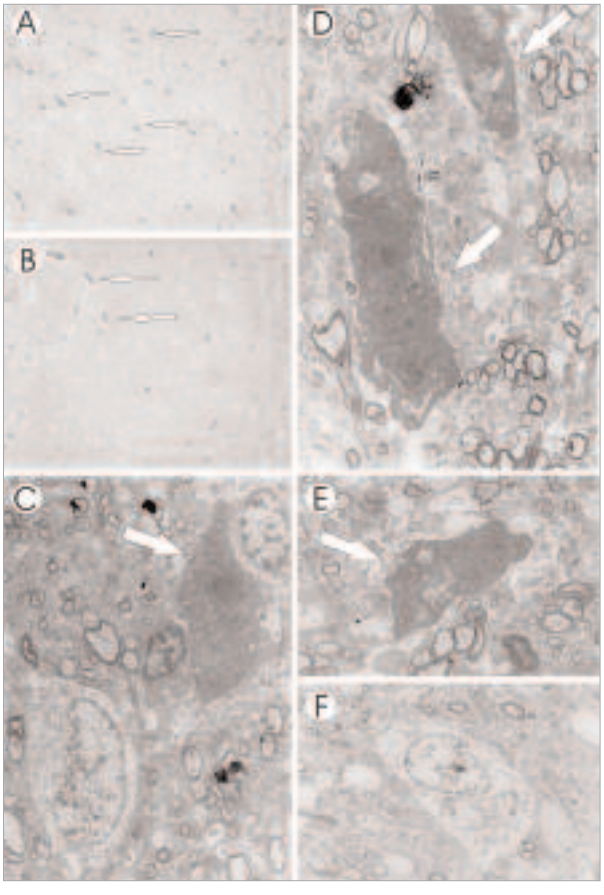

Electronic microscopy of apoptotic neurons in the hypothalamus of rats fed a high-fat diet (A-E). Non-apoptotic neuron from a control rat (F)

In the last decades there has been an astonishing increase in the prevalence of obesity and type 2 diabetes mellitus. Treatment based on modification of behavior and nutrition, and on the use of the few drugs available has not been sufficient to contain the advance of this epidemic. The characterization of the epithalamic mechanisms participating in the control of hunger and thermogenesis should allow for the identification of new targets for therapeutic approaches in these diseases. In the present project, multiple facets of the hypothalamic control of hunger and thermogenesis have been investigated. In the first stage, we carried out an analysis of the differential expression of RNAm in the hypothalamus of mice fed on a hyperlipidic diet. Modulations were detected in the mRNA expression of several inflammatory response proteins. In the next stage, we will investigate the role of TNF-α and IL-1β in the action of insulin in the hypothalamus and in the hypothalamic control of insulin secretion. We will further investigate the integration mechanisms between the hypothalamic signaling of IL-1β and insulin in a model of cancer.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

During the last 15 years obesity has become an epidemic phenomenon, affecting up to 30 % of the population of several regions of the world. As with other multifactorial diseases, the etiology of obesity is incompletely known. Multiple genetic loci have been identified as candidate regions encoding genes with potential role for the development of the disease, but some environmental factors, such as increased caloric intake and sedentary life style play an undisputed role in this context. The increased consumption of dietary fat is a hallmark of the modern occidental diet. Besides its intrinsic caloric value, dietary fats can act as inducers of inflammation in tissues such as muscle and liver. However, little was previously known about the role of dietary fats in the functional activity of the hypothalamus, the region of the brain responsible for controlling food intake and energy expenditure. The main objective of this project was to determine the effects of dietary fats on the function of the hypothalamus. For that we initially evaluated, by using a cDNA array, the effect of consumption of a fat-rich diet on the expression of genes in the hypothalamus. We found that 15% of the analyzed genes were regulated by the diet and that immune response genes were the most affected ones after functional clustering. Following that, we characterized the main cytokines expressed in the hypothalamus of rodents fed a high fat diet. This part of the study included the determination of several inflammatory and metabolic outcomes of the local actions of TNF-α and IL-1β. In addition, since dietary fats are complex and composed of several different types of fatty acids we evaluated the effects of isolated fatty acids in the hypothalamus. This study revealed that long chain saturated fatty acids are the most pro-inflammatory ones and that the inflammatory signal delivered by them depends on the recruitment of a specific receptor of the TLR family. At this moment we are engaged in the evaluation of the intracellular mechanisms that link the activation of TLR4 signaling with the control of the expression of inflammatory cytokines in the hypothalamus. Results obtained as part of this project may help find new targets for the treatment of obesity.

MAIN PUBLICATIONS

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