RELAZIONE DI METÀ PERIODO

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TIPOLOGIA DI BORSA RICEVUTA: Borsa per soggiorno all'estero

TIPOLOGIA DI RELAZIONE (es.: metà periodo o finale): Metà periodo

TITOLO DELLA RELAZIONE: Modulation of mitochondrial dynamics in ventromedial nucleus neurons: its pivotal role in glycidic metabolism

RELAZIONE:

Type 2 diabetes mellitus (T2DM) is a disease characterized by insulin resistance, inappropriate insulin secretion and activity. Over the past three decades, this metabolic pathology has reached epidemic proportions worldwide and its incidence will increase, becoming the seventh leading cause of death in 2030 (1).

In the last years, overwhelming evidences suggest a strong link between brain and liver in the regulation whole-body energy metabolism (2). Indeed, the hypothalamus, in particular its ventromedial nucleus (VMH), represents the primary site that manages biological information arising from peripheral organs to monitor the nutritional status of the organism (3). The development of the VMH architecture requires the presence and physiological activity of steroidogenic factor (SF)-1 neurons (4). This population of neurons plays a pivotal role in the regulation of metabolic features,

such as body weight and energy homeostasis, and together with proopiomelanocortin (POMC) and neuropeptide-Y-agouti-related-protein (NPY-AgRP) neurons constitutes the central regulatory circuit of metabolism located within the hypothalamus (5). Nevertheless, molecular mechanisms of SF1 neurons that are involved in managing metabolic changes keep still unclear.

The metabolic role of mitochondria as source of cellular energy is well known (6-8). These organelles produce ATP by using the electro-proton gradient made by electron transport chain and uncoupling proteins (UCPs) are involved in uncoupling the oxidative phosphorylation from ATP production. Beyond their physiological function, these proteins, including UCP2, have been recognized as key factors in managing host homeostasis and their defects lead to impaired mechanisms related to several disorders, such as inflammation (9), cancer (10) and metabolic syndrome (11).

In physiological conditions, mitochondria continually adapt in response to external changes by means the mechanisms of fission and fusion. Fission has a main function to divide damaged mitochondria from healthy cellular components, a process that is enhanced by several proteins, including dynamin-1-like protein (Drp1); while fusion, enhanced by mitofusin 1 and 2 (Mfn1 and Mfn2), allows to compensate eventual defects of malfunctioning mitochondria. Alterations of fusion and fission proteins are involved in onset of metabolic disorders. Sebastian et al. (12) demonstrated that Mfn2 deficiency is strongly linked to mitochondrial dysfunction and insulin resistance, caused by ER stress and the production of reactive oxygen species (ROS). Another *in vivo* study demonstrated the beneficial effects of metformin and resveratrol by protecting mitochondrial integrity through the inhibition of DRP1 activity in T2DM (13).

Despite the strong link between mitochondria dynamics and metabolic disorders, the role of mitochondrial proteins in VMH is still unclear. Toda et al. (14) have recently demonstrated that high concentrations of glucose increase mitochondrial fission and reduce ROS in VMH neurons by activating DRP1 and under UCP2 control.

The aim of this project is to investigate central mechanisms involved in control of glycidic homeostasis and the role played by mitochondrial proteins in VMH.

During the first half of this project, we generated mice ($Ucp2KO^{Sf1\text{-}Gfp}$) with selective deletion of UCP2 in VMH neurons by crossing Ucp2 floxed mice ($Ucp2^{fl/fl}$) with Sf1-cre-Gfp mice (already in our facility). As control mice, $Ucp2^{fl/+}$-Sf1-cre negative and $Ucp2^{fl/+}$- Sf1-cre-Gfp littermates were used.

To evaluate the role of Drp1 in VMH, we generated mice ($Drp1KO^{Sf1\text{-}Gfp}$) with selective deletion of Drp1 in VMH neurons by stereotaxic AAV-DREADD virus injection of Drp1 floxed mice ($Drp1^{fl/fl}$). In this case, these animals were bilaterally injected with the AAV2-GFP (as control) or AAV2-Cre-GFP ($Drp1KO^{Sf1\text{-}Gfp}$) virus into the VMH.

Furthermore, in first six months of his stay abroad, Dr. Adriano Lama learned other techniques of Prof. Diano's lab, including transcardially perfusion, c-fos immunostaining, DHE administration by tail injection that will allow him to carry out the second part of his main project.

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