

WE02-04

INCREASED BRAIN GLYCOGEN AFTER RECOVERY FROM ACUTE HYPOGLYCAEMIA SUGGESTS INVOLVEMENT IN HYPOGLYCAEMIA UNAWARENESSDuarte, J.M.¹, Morgenthaler, F.² and Gruetter, R.^{1,3}¹Center for Biomedical Imaging, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland²Cellular Imaging Facility, University of Lausanne, Lausanne, Switzerland³Departments of Radiology, University of Lausanne and University of Geneva, Lausanne and Geneva, Switzerland

Diabetes mellitus is characterised by hyperglycaemia that is associated with the occurrence of well described microvascular complications that affect different organs, which development is dependent on the duration of the disease and glycaemia control. For many individuals with diabetes, episodes of severe hypoglycaemia are a major complication of glycaemia control. Moreover, recurrent hypoglycaemia impairs mechanisms of defence against hypoglycaemia. Thus, diabetes patients display a progressive decay in the physiological counter-regulatory response, resulting in hypoglycaemia unawareness, and therefore prolonged exposure to hypoglycaemia insults may become lethal. One mechanism through which the brain adapts to hypoglycaemia may involve glycogen metabolism and its buffering effect on brain glucose concentrations. Conscious freely moving rats were submitted to hypoglycaemia below 35 mg/dL for 90 minutes by insulin administration, followed by a recovery period of 24 hours either under normoglycaemia or hyperglycaemia achieved by glucose infusion. Rats were then sacrificed by microwave fixation and glycogen concentration was determined in different brain regions. Control rats underwent the same treatment without the preceding hypoglycaemia period. Hypoglycaemia depleted brain glycogen content in the brain. In the cortex, glycogen concentration was increased by 65 ± 27% or 114 ± 16% when recovery from hypoglycaemia was performed under hyper- or normoglycaemia. Similar glycogen supercompensation was observed in the hippocampus but not in the hypothalamus and striatum. Brain glycogen concentration did not increase after 24 hours under hyperglycaemia without a preceding hypoglycaemia insult. In conclusion, supporting brain metabolism during recurrent hypoglycaemia periods, glycogen may have a role in hypoglycaemia unawareness.

WE02-05

GHRELIN REGULATES ENERGY BALANCE THROUGH HYPOTHALAMIC RECEPTORS IN A RAT OBESITY MODEL

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Feeding behavior and energy balance is maintained through integration of orexigenic and anorexigenic signals from the periphery in the hypothalamus, in particular in the arcuate nucleus. ARC neurons express anabolic Growth Hormone Secretagogue Receptor (GHSR), catabolic leptin (Ob-R) and Melanocortin 4 (MC4R) receptors, to detect ghrelin, leptin and α -MSH, respectively. Ghrelin is mainly produced in the stomach where, after acylation by O-acyltransferase (GOAT), may bind to GHSR. Acyl-ghrelin stimulates the gut-brain orexigenic axis to increase food intake and reduce fat mobilization, in contrast to leptin, which,

circulating at levels proportional to body fat, promotes the synthesis of the appetite suppressant α -MSH. To further understand how the neuroendocrine ghrelin system regulates energy homeostasis through the gut-brain-axis, we employed a novel approach to reduce the endogenous ghrelin levels through the removal of the stomach fundus by sleeve gastrectomy, the procedure of choice for morbid obesity. We developed a rat obesity model, where animals were fed a high fat diet for 12 weeks and then underwent sleeve gastrectomy or sham operation. All animals were then fed normal diet, and, when sacrificed one or three months later, ghrelin and GOAT in the stomach, GHSR, Ob-R and MC4R expression levels in the hypothalamus were assessed by semi-quantitative RT-PCR and immunodetection. We found that sleeve gastrectomy significantly decreased ghrelin message in the stomach when compared to sham- and non-operated animals. GOAT patterns followed that of ghrelin suggesting co-regulation of their expression as well as acylation of ghrelin. In the hypothalamus we observed decreased GHSR and Ob-R expression both at the message and protein levels, possibly due to lower acyl-ghrelin levels. As expected, lower fat and thus lower leptin levels, led to significantly lower expression of MC4R, upon withdrawal from the fat diet for at least 3-months. Our results indicate that ghrelin participates in the control of energy balance through the regulation of its own receptor GHSR, Ob-R and MC4R expression in the hypothalamus of obese animals.

WE02-06

IMPAIRED INSULIN SIGNALING IN A PRIMATE MODEL OF ALZHEIMER'S DISEASE: LINK WITH TYPE-2 DIABETESForny-Germano, L.^{1,2}, Bomfim, T.R.², Brito-Moreira, J.², Houzel, J.C.¹, Klein, W.L.³, Munoz, D.P.⁴, Ferreira, S.T.² and De Felice, F.G.²¹Federal University of Rio de Janeiro, Institute of Biomedical Sciences, Rio de Janeiro, Brazil²Federal University of Rio de Janeiro, Institute of Medical Biochemistry, Rio de Janeiro, Brazil³Northwestern University, Department of Neurobiology and Physiology, Illinois, USA⁴Queen's University, Centre for Neuroscience Studies, Ontario, Canada

Alzheimer's disease (AD) has been linked to defective brain insulin signaling, a proposed third type of diabetes (1, 2, 3). Although this intriguing connection between AD and diabetes has been suggested, a major unknown is the mechanism by which insulin resistance develops in AD brains. In type 2 diabetes, tumor necrosis factor- α (TNF- α) signaling stimulates c-Jun N-Terminal Kinase (JNK). This results in serine phosphorylation of the insulin receptor substrate (IRS-1), blocking downstream signaling and triggering insulin resistance (4). The link between diabetes and Alzheimer's disease was found in the ability of A β oligomers, toxins that accumulate in Alzheimer brain and instigate synaptic damage, to activate the JNK/TNF- α pathway leading to phosphorylation of IRS-1pSer636. The aim of this study was to investigate whether A β oligomers injected into the cerebral ventricles of adult cynomolgus monkeys are capable of triggering mechanisms similar to those described for type 2 diabetes. Our findings indicate JNK activation and increased levels of IRS-1pSer636 in primate hippocampus. They reinforce the link between diabetes and AD. Furthermore, considering the dearth of animal model systems that truly recapitulates the main features of Alzheimer's disease, this new non-human