Ελληνικά Διαβητολογικά Χρονικά 22, 2: 110-111, 2009

Insulin and brain

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Insulin is required for a variety of regulatory functions in multiple tissues such as induction of glucose uptake in skeletal muscle, suppression of hepatic glucose production, and inhibition of lipolysis in adipose tissue.[1] In addition to the classical insulin-sensitive tissues, the brain emerged as a major target of insulin action in rodents as well as in humans.[2] There is increasing evidence that adequate insulin receptor signaling is required for neuronal surviving,[3] the regulation of food intake,[4] determination of life span,[5] and adequate suppression of hepatic glucose production;[6] however, the insulin-specific activation patterns in cortical activity, their functional consequences and molecular mechanisms are much less clear. Insulin receptors are expressed all over the brain with its highest density in the hypothalamus, hippocampus, olfactory bulb, and cerebrocortical tissues where they display distinct functions[7] and promote tyrosine phosphorylation of proteins that engage various downstream signaling pathways including the insulin receptor substrate proteins, and the PI 3-kinase/AKT pathway.[8] We recently demonstrated by magnetoencephalography (MEG) measurements that insulin modifies cortical activity in lean humans, while obese subjects displayed insulin resistance.[2] In parallel, an increase in insulin levels led to an improvement in insulin receptor activation and cortical activity estimated by electrocorticography (ECoG) in mice,[9] and even in humans that are insulin resistant.[10,11] Moreover, the effect of insulin on cerebrocortical activity was modified by genetic alterations and aging.[2,12-14] To understand the functional consequences and molecular pathways of insulin action in the brain that are relevant in the pathophysiological state, we established electrocorticography measurements[9,15] in mice in combination with a cannula placed in the lateral ventricle to deliver substances directly intracerebroventricularly (icv). Thereby, insulin action can be linked to activation patterns in electrical activity in the mouse brain of lean and obese. By using this approach, the consequences of modulated insulin signaling in brain tissues with regard to cerebrocortical activity measured by electrocorticography in mice and finally behavior were detected and correlated to cortical activity determined by magnetoencephalography measurements in humans.

In our previous studies, insulin detemir was shown to activate the insulin signaling cascade in peripheral tissues to the same

extent as human insulin when applied in equipotent doses, however it reached higher concentrations in the brain when given intravenously (iv) into C57Bl/6 mice in comparable blood-glucose lowering concentrations.[9] Moreover, in human studies we demonstrated that insulin detemir was able to overcome cerebrocortical insulin resistance in obese subjects as it was sufficient to increase beta activity measured by magnetoencephalography during a hyperinsulinemic-euglycemic clamp, while human insulin failed to promote cortical activity in obese individuals.[2,10] Therefore, insulin detemir is supposed to be a tool that acutely activates the insulin si-gnaling cascade in the brain to a greater extent as human insulin, and even overcomes insulin resistance in obese due to acutely elevated insulin concentrations in the brain. In order to understand the physiological function of insulin action in human brain we recently studied the effect of nasal insulin on fMRI activation patterns after visual stimulation with food related pictures. Insulin modulates this response suggesting a potential role in a post prandial feedback mechanism regulating desire for food.

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