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Insulin, Insulin-like Growth Factor-1 and Neurodegeneration

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Dear Editor,

The role of insulin and insulin growth factor-1 (IGF-1) in the brain has been extensively revaluated in the last two decades. Several previous studies have shown that insulin is involved in a number of neurotrophic, neuromodulatory, and/or neuroendocrine effects, including the appetite control and energy expenditure and the interaction between insulin resistance, diabetes, and amyloid deposition in Alzheimer's disease (1, 2).

Insulin acts as a growth factor in the brain, providing a neuroprotective action by activating dendritic sprouting, regeneration and stem cell proliferation (3). Together with other peptides, like ghrelin or cholecystokinin, insulin is involved in the complex neuropeptidergic signaling network in the hypothalamus which regulates anabolic and catabolic balance (4). In general, insulin serves as a systemic feedback signal to reduce appetite and is therefore involved in body weight regulation and eating behavior. Insulin receptors in the brain are expressed at high levels in neurons, and to a lesser extent in glia and other areas of the brain (5). Impairment of insulin signaling in the brain has been linked to neurodegenerative diseases. Several rodent model studies of diet-induced obesity, using high-fat diet and/or fructose, found that insulin resistance leads to cognitive impairment as well as altered eating behavior (6-9). Moreover, mice with neuron-specific insulin receptor deletion show an increase in food uptake and body weight (10). On the other hand, restoration of insulin receptors in the brain of mice with tissue-restricted insulin receptor expression maintains energy homeostasis and prevents diabetes (11). In addition, patients with type 2 diabetes (T2D) have an increased risk of developing Alzheimer's disease (AD) (1, 12), since insulin resistance can promote the production and secretion of amyloid ß-peptide, a hallmark of AD (13). Impairment of insulin signaling in the brain has also been shown to be a factor in central nervous system dysfunctions such as Huntington's disease or parkinsonism (14, 15). Therefore, the increased risk of cognitive dysfunction in elderly diabetic patients is probably a consequence of the synergistic interaction between diabetes-related metabolic derangements and the structural and functional cerebral changes due to normal aging processes (16, 17).

A recent study published in 2010 by Tafreshi et al. (18), showed increased levels of IGF-1 protein in the brain of insulin-resistant rats compared to healthy controls. The study investigated the expression of IGF-1 protein in different areas of the brain including the brain stem, cer-

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ebellum, hippocampus, and thalamus in Wistar rats that consumed 10% fructose in their drinking water for at least 4 months. Similar results were reported in a study conducted by Moroz et al (19), where increased levels of IGF-1 mRNA were measured in the brain of mice fed a high fat diet in a model of Alzheimer-type neurodegeneration. The impact of increased fructose consumption on neureodegenerative processes is poorly understood. Fructose is a growing component of the American diet through the consumption of processed foods, baked goods, and especially sugar sweetened beverages. Due to a significant increase in fructose consumption per capita over the past two decades, it has become the target of a great deal of investigation regarding its obesogenic and metabolic effects (20-23). Fructose consumption is known to induce hypertension, impair glucose tolerance, and insulin resistance in animal models, and in addition may be preferentially converted into triglycerides in the liver (22-24). Fructose does not stimulate insulin or leptin secretion, and the consequences of reduced satiety following elevated fructose intake may contribute to obesity development in both humans and animals (25). Insulin stimulates the release of IGF-1 (26), but the association between insulin and IGF-1 secretion following fructose intake is not well characterized, and its role in neurodegenerative processes is currently unknown. This finding opens up new considerations about the regulation of insulin/IGF-1 signaling in the brain. Hyperglycemia induces increased peripheral utilization of insulin, resulting in reduced insulin transport into the brain; therefore it might be possible that increased levels of IGF-1 in the brain arise as a compensatory mechanism to prevent disruption in metabolism and survival of neurons. This mode of action of IGF-1 in the brain mimics the effects of insulin itself, not surprising given the high degree of homology between insulin and IGF-1. It has been postulated that IGF-I is a tonic regulator of insulin sensitivity through its direct interaction with insulin receptor homodimers; however we still don't understand the significance of these hybrid receptors (27). The action of IGF-1 in insulin sensitivity has been demonstrated in several studies. Administration of IGF-1 to healthy humans results in lowered glucose levels, but to a much lesser extent relative to insulin (28). In patients with extreme insulin resistance, IGF-1 administration improves insulin sensitivity and carbohydrate homeostasis (29). However one of the major problems in interpreting the action of IGF-1 in the brain from this current study is the missing picture of the other integrated nutritional, metabolic and endocrine signals, including leptin and growth hormone (GH), which have an impact on the circulating insulin level, the transport of insulin from the blood to the brain, and on IGF-1 regulation. Thus, the intriguing findings by Tafreshi et al. (18) will hopefully stimulate additional studies that include GH, leptin, adiponectin and other metabolic regulators involved in insulin resistance, to increase understanding of the impact that insulin resistance has on neurodegeneration.

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