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COMMENT ON GRAY ET AL.

Insulin Regulates Brain Function, but How Does It Get There? Diabetes 2014;63:3992–3997

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Gray et al. (1) reviewed findings on the important role of insulin in the regulation of the brain functions related to feeding behavior, energy stores, and cognition. They raised key questions on mechanisms and efficacy of insulin delivery routes to the various areas in the brain. The authors discussed both peripheral (intravenous) and central (intranasal and intracerebroventricular) routes of insulin administration to the central nervous system (CNS).

They did not mention, however, another approach to deliver insulin to the brain by intracranial or intrathecal transplantation of pancreatic islets. In contrast to insulin injections, the CNS-grafted pancreatic islets release insulin directly into the extracellular fluids of the brain and spinal cord according to metabolic requirements. In addition, islets secrete other pancreatic hormones (e.g., glucagon, somatostatin, amylin) and various neurotrophic factors that play an important role in neuroprotection. Insulin and other hormones derived from grafted islets cross the blood-brain barrier and reach the peripheral targets (liver, muscle, and adipose tissues) participating in regulation of glucose homeostasis (2).

Recently, we suggested that pancreatic islets intracranially grafted into the rat subarachnoid space may serve as a promising tool for insulin delivery to the brain for treatment of cognitive dysfunctions (2,3). To test this hypothesis, islets were grafted into the subarachnoid space around the olfactory bulb and prefrontal cortex of rats displaying schizophrenia-like behavioral dysfunctions induced by exposure to dizocilpine, an uncompetitive antagonist of the N-methyl-D-aspartate receptor. The CNS-grafted islets significantly attenuated the dizocilpine-induced hyperresponsive behavior in the open field test and improved spatial learning and memory in the water maze test. Importantly, the CNS-grafted islets significantly increased insulin concentration in the hippocampus and frontal cortex without alteration of peripheral glucose homeostasis (4).

Gray et al. (1) highlighted the importance of a rational consideration of therapeutics involving the delivery of insulin to the brain. In this context, comparison between clinical intrahepatic islet transplantation in patients with diabetes and potential islet transplantation in the CNS of normoglycemic patients with cognitive dysfunctions suggests that the CNS as a transplantation site provides significant advantages in terms of the small amount of transplanted islets, highly oxygenated microenvironment, and immune-privilege properties. On the other hand, metabolically regulated continuous delivery of insulin to the brain raises several questions regarding possible alterations in brain insulin resistance, feeding behavior, and effect on preexisting cancer cells.

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The authors of the cited article did not feel a response was necessary.