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Is diabetes a disease of the brain?

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Is diabetes a disease of the brain?

Guest Column

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American Diabetes Association defines diabetes mellitus as a group of metabolic diseases characterized by hyperglycemia resulting due to the defects in insulin secretion, insulin action, or both. Prolonged diabetes is associated with dysfunction, and failure of various organs, especially the kidneys, heart, nerves, eyes and blood vessels. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.

Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction.

Among the two types of diabetes - insulin dependent diabetes mellitus (IIDM) called type 1 diabetes, and the insulin not dependent diabetes mellitus (NIIDM) called type 2 diabetes - NIIDM is prevalent among 90-95 percent of diabetic population. One of the major findings is that most of the patients suffering from type 2 diabetes are obese, which also causes insulin resistance to some level.

Researchers say people with variations in certain "obesity genes" tend to eat more meals and snacks, consume more calories per day and often choose the same types of high fat, and sugary foods. Recent studies suggest that specific areas of

Hypothalamus may play a significant role in maintaining plasma glucose and insulin secretion. Researchers also discovered that individuals with BDNF variations consumed more servings from the dairy and the meat, eggs, nuts and beans food groups. They also consumed approximately 100 more calories per day. This indicates a connection of stimuli induced during growth of brain with diabetes. Brain is rich in poly unsaturated fatty acids (PUFAs) that constitute 30 percent to 50 percent of the total fatty acids in the brain.

Diabetes, obesity and neurological disturbances, most often show co-occurrence. Recent research published in *Bioinformation* indicated the role of Butyryl cholinesterase (BCHE) in diabetes, obesity and neurological disorders by performing a comparative analysis with Neuroligin (NLGN2), a protein belonging to the same family. BCHE also has its role in glucose regulation, lipid metabolism and nerve signaling.

Inadequate concentrations of PUFA during the third trimester of pregnancy to two year post term will pose to higher Tumor necrosis factor- Î± Concentration. In turn, higher TNF Î± may damage the VMH neurons that leads to type 2 diabetes at a later stage of life. Research also suggested that low grade systemic inflammation also plays a significant role in pathogenesis of type 2 diabetes. It is a well known fact that decrease in the number of insulin receptors, defects in the function of insulin receptors, and insulin lack or resistance in the brain leads to the development of type 2DM, even when pancreatic Î²-cells are normal.

Diabetes mellitus is very common and is a fast emerging epidemic in India. Deficiency of BDNF and PUFA is well documented in type 2 diabetic conditions by several groups throughout the world. PUFAs such as AA (Arachidonic acid), EPA (Eicosapentaenoic acid), and DHA (Docosahexaenoic acid) can give rise to anti-inflammatory and cytoprotective compounds, such as lipoxins (LXs), resolvins and protectins that could protect pancreatic Î² cells from the cytotoxic action of chemicals such as alloxan and streptozotocin. Recent studies at my laboratory on Indian diabetic patients indicated low BDNF levels in them. Both Insulin and PUFA forms a potent neurotransmitter which carries the information from VMH neurons to the pancreatic Î²-cells and thus control their insulin secretion.

Adequate amount of insulin and insulin receptors in the brain control obesity, Hyperphagia and helps maintaining normal glucose levels and controlling inflammation. This surely opens up a new arena "to control type 2 diabetes mellitus, brain can play an important role since hypothalamus of brain is known to have good amount of insulin receptors".

Therapies available

Insulin therapy is often an important part of diabetes treatment in around 30 percent cases of diabetes patients. Duration of diabetes decides the date of insulin treatment. Patients with prolonged history of diabetes are more likely to start insulin treatment at some point of time. In the early stages, diabetic patients are managed with modified lifestyles such as feeding habits, initiating exercises, etc. and oral hypoglycemic agents or injections of a Glucagon-like peptide-1 (GLP1) analogue either alone or in combination with oral medication. Some percentage of patients later will be dependent on insulin therapy like the type 1 diabetes patients. Insulin is inactivated by the digestive enzymes in the gut and can't be taken by mouth therefore most commonly it is given as a subcutaneous injection into the thigh, buttocks, abdomen or upper arm. Patients with advanced diabetic condition and fluctuating glucose levels are at higher risk of hypoglycemia with a risk of complications like falling and accidents.

Recent advancement in medical sciences has introduced Laparoscopic surgery. Guidelines from the National Institutes of Health say the surgery can be offered to people with a body mass index, (BMI) of over 40, or over 35 if the person has diabetes or another illness related to obesity. The American Diabetes Association also says people with type 2 diabetes and a BMI of over 35 should consider the surgery. Someone 5 feet 6 inches tall with a BMI of 35 would weigh 215 pounds and a BMI of 40 will weigh 245 pounds. This is a costly affair and everybody can't afford it but it's a ray of hope for the future.

Hope for an oral and long lasting Diabetic Therapy

Several studies have quoted that BDNF injections in diabetic mice have lowered glucose levels. BDNF has lasting effect on blood glucose levels and efficacy can be maintained with less frequent administration of BDNF in the body. One of the research groups has also claimed that BDNF administration prevents pancreatic exhaustion in diabetic mice.

One needs to understand the mechanisms of action of BDNF with pancreas and changes in the structure of BDNF reported in Humans and related model organisms. Research is on to understand the mechanisms of Î²-cell protective action of BDNF, PUFAs and BDNF + PUFAs complexes. One mechanism could be the suppression of pro-inflammatory cytokines production by BDNF, PUFAs and BDNF + PUFAs complexes. Initial studies at my lab also observed that the levels of BDNF are found to

be higher in the Type II diabetic patients doing regular exercise as compared to the patients who never exercise. G196A mutation has been widely studied worldwide but most of them don't support its involvement with type 2 diabetes.

Recent study published in March 12 in *Nature Medicine* reveals that there may be a way to stimulate expression of that gene to treat obesity caused by uncontrolled eating. The brain-derived neurotrophic factor (BDNF) governs the brain neurons to effectively pass the signals to body when one shall stop eating. Neurons can't communicate to produce the right signals required for the body and the person slowly becomes obese if there is a problem with the BDNF gene. Obese persons are at the highest risk of developing diabetes and many of them are already prediabetic. They realize this when they develop diabetes. A drug with a capacity to stimulate Hypothalamus can be effective here.

This important field of neuropathic factor Research has attracted lot of interest in the recent years. Structure based drug discovery and application of computational intelligence techniques in creating drug libraries and selection of leads may open up new horizons in another antidiabetic drug Research. There is great hope that soon we may physically have something which can replace insulin for treating the diabetes orally.