BRIEF COMMUNICATION

Is Diabetes Pre-coded in the Brain? Role of Hypothalamus, Addiction Network and Social Cognition

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ABSTRACT

The hypothalamus, the master regulator of circadian rhythm, in association with peripheral clocks, play crucial roles in glucose metabolism. Impairment in cerebral sensing, uptake and processing of glucose has been suggested in various animal and human diabetic models. Diabetes Mellitus has been largely superseded by the discovery of insulin and insulin resistance. Expanding horizons of knowledge of the roles of the hypothalamus in glucose metabolism and the overlapping neural pathways of sugar addiction with other classically described substance and behavioral addictions networks have again thrown some light on the cerebral theory of DM pathogenesis.

Keywords: Diabetes mellitus, Hypothalamus, Brain, Cognitive impairment

Introduction

Evidence in favor of multifaceted afflictions of diabetes mellitus (DM) on the brain has been burgeoning. Contemporary studies exhibited the definitive and deleterious impact of DM on the brain leading to premature brain aging and manifestations ranging from cognitive impairment, and behavioral alteration to focal neurological deficits.[1] Authors, herein, want to decode the inverse relationship. Although, the brain has been regarded as one of the key organs in the classic "ominous octet",[2] its exact role in the pathophysiology of DM is yet to be fully decrypted.[3] The mechanistic pathways by which psychoneurotic traits, an established risk factor for the development of DM and maintenance of glycemic equipoise, need further elucidation.[4,5] Is there a possibility of the beta-cell failure to be prospectively orchestrated by altered glucose-sensing machinery residing in the brain? Are there certain pre-existing pre-destined frameworks in the brain responsible for the future development of DM? How can certain brain-behavior relationships lead to the development of DM in later life?

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Cerebral Pathogenesis of Diabetes – Role of Hypothalamus, Midbrain and Brainstem

Hypothalamus has long been considered the nodal player in the regulation of satiety, body weight and glycemic status since 1854 when Claude Bernard reported that a lesion in the floor of the fourth ventricle in dogs altered glucose levels, thereby presenting the first evidence of the brain's role in glycemic regulation.[3] Works in *Drosophila* have found that there are key glucose-sensing neurons which orchestrate insulin and glucagon secretion downstream.[3,6] A case has been made regarding the common evolutionary origin of beta cells and brain.[7] The key parameters of

glycemic control viz. satiety, obesity, insulin secretion and insulin resistance which predict the future risk of development of DM have now been proven to be governed by the hypothalamus.[3,8] The hypothalamus, the master regulator of circadian rhythm, in association with peripheral clocks, play crucial roles in glucose metabolism.[9,10] Impairment in cerebral sensing, uptake and processing of glucose has been suggested in various animal and human diabetic models.[11-14] One of the most recent additions to the understanding of cerebral pathogenesis of diabetes is "glucose effectiveness", the phenomenon through which glucose promotes its own disposal using central K_{ATP} channels (independent of insulin).[15] Analogous to the leptin resistance in obesity, DM which is also a closely related metabolic disease, can be viewed as a cerebral glucose-resistant state which uplifts the glycemic set-point to set in a new steady-state leading to the generation of a vicious cycle of glucotoxicity and progressive beta-cell failure.[3,16] The role of the brain in glucose metabolism is further strengthened by the evidence that intracerebroventricular administration of leptin ameliorates hyperglycemia by insulin-independent pathways.[17,18] Similarly, intracerebroventricular injection of the fibroblast growth factor (FGF) family of proteins, especially FGF-1, 19 and 21 is capable of reversing hyperglycemia in rodents.[19-21]

Addiction Circuitry and Diabetes

Smoking, alcohol and other substance abuse have been causally linked to the pathogenesis of DM based on epidemiological proofs and identifying downstream cascades of deleterious molecular mechanisms. Addictive behavior has a definitive role in the future development of DM, governed by brain networks (addiction and reward circuits) as they share a common genetic susceptibility region afflicting the cerebro-pancreatic network.[22] Food addiction has been linked to the development of type 2 DM independent of age, sex, body mass index and other comorbidities including obesity.[23] Contextually, the concept of sugar addiction and its causative role in obesity, DM and other chronic metabolic diseases has already gained popularity in the public health arena.[24] Studies already have demonstrated that sugar addiction involves the ventral tegmental area (VTA) and nucleus accumbens (NAc), the same designated brain network involved in substance and behavioral addiction. Dopamine is the key neurotransmitter responsible for food (sugar) addiction with contributions of acetylcholine and opioid neurotransmitters as well.[24,25] Sugar addiction can cause glucotoxicity, rebound insulin release and beta-cell exhaustion in the long-term with an increased risk of developing insulin resistance and eventually DM in the future.[26] It has also been observed reciprocally during treatment of DM and subsequent counseling regarding the risk of development of hypoglycemia; patients often take sugar binge without any definitive evidence of hypoglycemia. This is an indirect reflector of addictive behavior (sugar addiction) which significantly interferes with the achievement of proper glycemic control.[27,28] Internet addiction, the most common modern form of behavioral addiction[29] has been associated with a sedentary lifestyle,[30] which is the harbinger of incident diabetes. In a reverse way, researchers have also untangled the intricate association of increased prevalence of addiction among diabetics compared to nondiabetic individuals further strengthening the role of an in-built "addiction network" in the brain much before the development of DM.[31]

Parenting, Personality Development and Risk of Developing Diabetes Mellitus

Personality is the supreme reflection of cognitive and behavioral excursion in a patterned way based on learning and experience in environmentally triggered situations and personal space issues.[32] Parental personality and parenting style have dominating effect on the lifestyle and food habits of their children.[33,34] Type A personality of parents and parental stress being transferred to their offspring lead to faulty food habits, altered sleeping patterns, decreased play time, competitive attitudes, and a sedentary lifestyle from a very early phase of life.[35] This prodiabetic personality, behavior and lifestyle of the child and that of the family, implant the seeds of a faulty metabolic milieu deeply inside the evolving nascent networks of the brain of these children, earlier in life much before the development of glycemic dysregulation.[36]

Conclusion

Although the discovery of neural control of glycemia dates back nearly 200 years, the concept that the brain is the central player in the pathogenesis of DM has been largely superseded by the discovery of insulin and insulin resistance. Expanding horizons of knowledge of the roles of the hypothalamus in glucose metabolism and the overlapping neural pathways of sugar addiction with other classically described substance and behavioral addictions networks have again thrown some light on the cerebral theory of DM pathogenesis. Personality traits of children and

their parents, parenting and lifestyles are crucially and intricately related to brain functions and may have the potential to cause DM in later life. Keeping in an analogy of purely neurological and psychiatric illness that occurs in an already compromised brain, the seeds of diabetes mellitus, obesity and metabolic syndrome per se are ingrained in the fertile soil of an already precarious brain.[37] Lastly, there has been a long-awaiting dearth of artillery in the therapeutic armamentarium of DM which is directed at the brain and the authors anticipate that this is an area for an Odysseus voyage in future research.[38,39]

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