ACADEMIA | Letters

Does a brain dysfunction cause diabetes mellitus?

John Young, Professor emeritus, Howard University College of Medicine, Washington DC

In diabetes mellitus (DM), elevated levels of blood glucose cause serious damage to many organ systems (cardiac, renal, ophthalmological). In type I diabetes, an attack upon insulin producing cells of the pancreas by cells of the immune system causes a deficiency in insulin secretion. In the absence of insulin, muscle and liver cells fail to remove glucose from the bloodstream. In the more common type of diabetes, type II diabetes, insulin secretion may be normal or even elevated, but liver and muscle cells fail to respond to insulin and do not take up glucose from the bloodstream properly. Type II DM generally arises during middle age and can be regarded as a disorder of aging. The causes of this aging-related insulin resistance and the depressed uptake of glucose into muscle and liver are uncertain (1).

New evidence points to a crucial role of a brain region called the hypothalamus in the development of type II DM. For one thing, a gene called Dusp8 is linked with an increased risk for type II DM (2). This gene codes for a protein that regulates neuronal signaling in the hypothalamus.

Also, infusions into the hypothalamus of a hormone called leptin normalize blood glucose in diabetic animals (3). This suggests that activation of hypothalamic cells by leptin has a crucial role in maintaining normal levels of blood glucose. Thus, both the endocrine cells of the pancreas AND cells in the hypothalamus appear to have a major influence upon the control of blood glucose.

Hypothalamic neurons likely exert their controlling influence upon blood glucose via projections to neurons of the autonomic nervous system that are found in the spinal cord. Autonomic innervation of liver and muscle cells stimulates an increased uptake of glucose. In diabetic humans, the reactivity of the autonomic nervous system to changes in blood glucose is abnormal (4, 5).

Academia Letters, August 2021 ©2021 by the author — Open Access — Distributed under CC BY 4.0

Corresponding Author: John Young, jandpyoung4444@gmail.com
Citation: Young, J. (2021). Does a brain dysfunction cause diabetes mellitus? *Academia Letters*, Article 3079. https://doi.org/10.20935/AL3079.

Leptin-sensitive, glucose regulating neurons become resistant to leptin during aging or during exposure to a high-fat diet. These leptin resistant neurons fail to restrain food intake, obesity, and blood glucose. The reasons for this lowered responsiveness to leptin are uncertain and are part of the puzzle of the causes of type II DM (6).

Blood glucose levels can also be normalized in diabetic rodents by a single intrahypothalamic infusion of Fibroblast Growth Factor 1 (FGF1), an effect that persists for months even in severely diabetic animals. This is accomplished by a modulation of the function of accessory brain cells called astrocytes (7, 8).

Which specific astrocytes respond to FGF1, and how is this astrocyte response translated into an altered activity of neural circuits that regulate blood glucose? Hypothalamic astrocytes that produce Fatty Acid Binding Protein 7 (FABP7) are unusually abundant in the area of the hypothalamus containing leptin-sensitive neurons. These astrocytes are in close contact with leptin-sensitive neurons, influence their function, and regulate leptin sensitivity (9, 10, 11). An abnormal function of FABP7+ astrocytes thus may contribute to the leptin resistance that appears during aging and during exposure to high-fat diets. Perhaps FGF1 may normalize hypothalamic function by reversing abnormalities in FABP7+ astrocytes. However, what would provoke an abnormal function of FABP7+ astrocytes during aging and the development of diabetes in the first place?

In fact, likely causes for aging-related abnormality in FABP7+ astrocytes have already been identified. During aging, these cells develop cytoplasmic granules derived from degenerating mitochondria. This mitochondrial degeneration is likely due to the oxidative stress of the heightened amounts of fatty acids that are taken up by these cells and oxidized within mitochondria (12, 13). It seems likely that a pathological degeneration of mitochondria in these cells would compromise their normal functions. Thus, these cells may represent a mechanistic link between aging, high fat diets, and the development of leptin resistance in the hypothalamus.

Astrocytes with these degenerating mitochondria are also unique in that they possess high capacity GLUT2 type glucose transporter proteins (14). These glucose transporters are the same type as those found in glucose-sensing, insulin-producing cells of the pancreas.

Recent data show that astrocytes function as glucose sensors in the brain. Astrocytes, and not neurons, are now known to first respond to changes in tissue levels of glucose; moreover, if astrocyte function is experimentally depressed, neurons no longer respond to glucose (15). These data suggest that FABP7+ astrocytes regulate the responsiveness of hypothalamic neurons to changes in blood glucose. This is another way by which FABP7+ astrocytes may make an important contribution to the hypothalamic control of blood glucose.

Much of this information on astrocytes with damaged mitochondria has been obtained

©2021 by the author — Open Access — Distributed under CC BY 4.0

Corresponding Author: John Young, jandpyoung4444@gmail.com
Citation: Young, J. (2021). Does a brain dysfunction cause diabetes mellitus? *Academia Letters*, Article 3079. https://doi.org/10.20935/AL3079.

from studies on experimental animals. However, since the same type of astrocyte has been identified in the same region of the human hypothalamus, it is plausible that these findings can be extended to an understanding of human brain function (16).

In summary, specialized astrocytes in the hypothalamus appear to regulate the function of glucoregulatory neurons. It is possible that the age-related degenerative changes in the mitochondria of these cells may compromise their functions and contribute to the aging-related pathogenesis of type II diabetes mellitus.

References

1. Sangwung P, et al., Mitochondrial dysfunction, insulin resistance, and potential genetic implications. *Endocrinology* 2020; **161**:bqaa017

2. Schriever SC, et al., Type 2 diabetes risk gene Dusp8 regulates hypothalamic Jnk signaling and insulin sensitivity. *J Clin Invest* 2020; **130**:6093-6108.

3. German JP, et al., Leptin activates a novel CNS mechanism for insulin-independent normalization of severe diabetic hyperglycemia. *Endocrinology* 2011; **152**:394-404.

4. Heni M, et al., Central insulin administration improves whole-body insulin sensitivity via hypothalamus and parasympathetic outputs in men. *Diabetes* 2014; **63**:4083–4088.

5. Lundqvist MH, et al., Altered hormonal and autonomic nerve responses to hypo- and hyperglycaemia are found in overweight and insulin-resistant individuals and may contribute to the development of type 2 diabetes. *Diabetologia* 2021; **64**:641-655.

6. Salazar J, et al. Is "leptin resistance" another key resistance to manage type 2 diabetes? *Curr Diabetes Rev* 2020; **16**:733-749.

7. Alonge KM, et al. Brain control of blood glucose levels: implications for the pathogenesis of type 2 diabetes. *Diabetologia* 2021; **64**:5-14.

8. Bentsen MA, et al., Transcriptomic analysis links diverse hypothalamic cell types to fibroblast growth factor 1-induced sustained diabetes remission. *Nat Commun* 2020; **11**:4458.

9. Adlanmerini M, et al., Hypothalamic REV-ERB nuclear receptors control diurnal food intake and leptin sensitivity in diet-induced obese mice. *J Clin Invest* 2021; **131**:e140424

 ©2021 by the author — Open Access — Distributed under CC BY 4.0

Corresponding Author: John Young, jandpyoung4444@gmail.com
Citation: Young, J. (2021). Does a brain dysfunction cause diabetes mellitus? *Academia Letters*, Article 3079. https://doi.org/10.20935/AL3079.

10. Yasumoto Y, et al., Glial fatty acid-binding protein 7 (FABP7) regulates neuronal leptin sensitivity in the hypothalamic arcuate nucleus. *Mol Neurobiol* 2018; **55**:9016-9028.

11. Young JK, Anatomical relationship between specialized astrocytes and leptin-sensitive neurons. *J Anatomy* 2002; **201**:85-90.

12. Young JK, et al., Immunoreactivity for brain fatty acid binding protein in Gomori-positive astrocytes. *Glia* 1996; **16**:218-226.

13. Schmidt SP, Misfolding of short-chain acyl-CoA dehydrogenase leads to mitochondrial fission and oxidative stress. *Mol Genet Metab* 2010; **100**:155-62.

14. Young JK, McKenzie JC. GLUT2 immunoreactivity in Gomori-positive astrocytes of the hypothalamus. *J Histochem Cytochem* 2004; **52**:1519-1524.

15. Rogers RC, et al. Response of catecholaminergic neurons in the mouse hindbrain to glucoprivic stimuli is astrocyte dependent. *Am J Physiol Regul Integr Comp Physiol*. 2018; **315**:R153-164.

16. Young JK, Neurogenesis makes a crucial contribution to the neuropathology of Alzheimer's disease. *J Alzheimer's Dis Reports* 2020; **4**:365–371.

 ©2021 by the author — Open Access — Distributed under CC BY 4.0

Corresponding Author: John Young, jandpyoung4444@gmail.com
Citation: Young, J. (2021). Does a brain dysfunction cause diabetes mellitus? *Academia Letters*, Article 3079. https://doi.org/10.20935/AL3079.