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Can the Glucose Central Control System Dysfunctions Induce Diabetes Mellitus?

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Abstract

We study afresh how the glucose control system anomalies impact the organicity of the glucose homeostasis and build up events of persistent hyperglycemia and diabetes mellitus. We have used critically the state of art literature related to the subject, in order to cross, to compare, and to organize the relevant contents to create a logical and consistent support to the finds. We show that it is consistent to assume that persistent hyperglycemia and diabetes mellitus can have precursors not only in pancreas, but also in brain, mainly induced by noxious dysfunctions of hypothalamus sensor neurons circuits and external noxious elements, causing pancreas overload, and the consequent exhaustion—overburden.

Keywords

Brain, Hypothalamus, CNS—Central Nervous System, Sensor Neuron Circuits, Glucose Central Control System, External Noxious Elements, Juvenile Persistent Hyperglycemia, Diabetes Mellitus, Homeostasis, Euglycemia

1. Introduction

Persistent hyperglycemia can have a variety of causes and not properly treated can evolve into diabetes mellitus [1] [2] [3].

The standard model to explain the acute persistent hyperglycemia causing type 1 diabetes mellitus (T1DM) is pancreas failures due to the destruction of the beta cells by the immune system. This causes the production of insulin by the pancreas to shut down and so the persistent hyperglycemia and the T1DM set up [1] [2] [3].

Persistent hyperglycemia is also related to other types of diabetes such T2DM, diabetes mellitus type 3 and others [1]. These types are called non-insulin-dependent diabetes. The pancreas might be dysfunctional or overburdened, but not

completely "**shutting down**", or the insulin is not properly absorbed by cells due to a variety of cell dysfunctions.

The main focus here is to address afresh the T1DM problem. It is a general common sense that T1DM is caused by pancreas immune attack disease, in this scenario nothing is said about the possible pancreas exhaustion due to overload caused by, for instance, the brain central control dysfunctions. We guess here that pancreas exhaustion—overburdened and dysfunctional due to strain stress might be treated in a more straightforward manner since all that the system needs is to "rest" or insulin load production reduction, but the dysfunction due to pancreas beta cell destruction is a more complicated situation to treat and it would be necessary to induce beta cells to grow using genetic tools, and so the subject in this scenario is considered with an uncurable disease [4] [5]. Also, the naturally reduced volume of beta cells in the pancreas and the late discovery of the disease make it even more complicated to **treat the subject** since avoiding the complete cell volume destruction and so the complete insulin dependence of **makes it** an almost impossible task to doctors fulfills.

We want to address afresh the problem of persistent hyperglycemia induced by dysfunctions of the glucose central control system carried out by hypothalamus sensor neuron circuits, trying to connect this dysfunction with the persistent hyperglycemia that can set temporarily or permanently.

We show here the importance of considering a new paradigm for addressing the overall aspects of the glycemic dysfunctions. Undeniably, the insulin paradigm represents an immeasurable advance in the field of glycemic balance in diabetic patients. However, as in all fields of knowledge, new evidence of causes to diabetes is forming on the horizon and at some point, they will impose themselves. The need for a new and more efficient treatment for T1DM is mandatory, especially because the artificial insulin paradigm by itself is not enough to restore the natural homeostasis and balance to the body for long periods, and this ends up giving rise to several very serious body complications due to dangerous short period glycemic fluctuations.

The current state of the art and paradigm followed to access the epidemic of T1DM consider the glycemic out of balance as an autoimmune disease characterized by the destruction of insulin-producing pancreatic beta-cells, where the loss of beta-cells leads to insulin insufficiency and so a severe persistent hyperglycemia sets up if insulin is not intaken. The importance of insulin is not the question, and in this scenario, the importance is clearly stated in the summary of the "The Nobel Prize in Physiology or Medicine of 1923", which was awarded jointly to Frederick Grant Banting and John James Rickard Macleod "for the discovery of insulin":
https://www.nobelprize.org/prizes/medicine/1923/summary/ [1]. The main point is that insulin can indeed recover the euglycemia, but artificially, and with severe fluctuations of glycemia sometimes. In the above scenario, the source cause of T1DM is left only to an autoimmune disease driver.

Also today, we are all exposed to intense social and information changes

which induce the intense need for cognition, we also face severe environmental changes, overwhelming electromagnetic field exposure, and a great deal of chemical and pharmacological elements ingestion, all of these causing extreme body stress and overload that drives strains everywhere in our body. Since the main window of all that is our brain and considering that the brain is the central control of body's general homeostasis, not only of the glucose, coupling those noxious elements to brain's functioning is a must for any understanding of persistent hyperglycemia, and might well be that many idiopathic diseases, including idiopathic diabetes, could be better understood using this integrated approach.

Needless to say that the old insulin paradigm of T1DM cannot help one to assess all the aspects of the hyperglycemia induced by internal and external noxious elements that are not directly related to the immune system.

The best shooting to establish a new/alternative paradigm for T1DM research and treatment is to consider the presence of internal and external stressors and the consequent dysfunctions that they can induce in the glucose central control system. It is therefore in order to look at the problem of T1DM in a more systematic and coupled way (Brain—Pancreas axis). The glucose central control is carried out by the hypothalamus and its sensor neuron circuits, and the dysfunctions of it can indeed cause the onset of diabetes mellitus apart or in addition to autoimmune scenarios. This new possibility should not be neglected even if the insulin intake approach is used by almost all clinics as the final answer to control the T1DM persistent hyperglycemia.

To evaluate the performance of the sensor neuron circuits must be as important as to look for dysfunctions in the immune system related to the pancreas. For the sake of clinical evaluation completeness, both approaches must be considered to access the T1DM causes.

In order to anchor this thesis, we want to bring together the content published by several respected medical journals in order to show that indeed persistent hyperglycemia must also be associated with defectiveness in CNS control. The expected findings might well open new lines of development of treatments that could offer better and/or alternative results in the control of hyperglycemia. What we envisage is that adjusting the neuron control system, it would bring back the system to euglycemia, preventing pancreas overload and the consequent onset of hyperglycemia.

This paper is organized as follows. In Section II, we discuss the glucose control system and possible novel aspects and peculiarities. In Section III, we show how dysfunctions of this control system might affect the homeostasis and the euglycemia and create a rote not only to hypoglycemia but also to hyperglycemia and T1DM. In Section IV, we present the conclusions. The references follow.

2. Brain Glucose Control System

The glucose homeostasis and its management system are kept by a complex

coupled nonlinear system of organs, hormones, and electric circuits. The complexity of this system can be exemplified by the action of the astrocyte neurons which act via the autonomic system connections with the liver, pancreas, and adrenal gland and so to maintain the glucose homeostasis [1] [6]-[20].

It is not possible to talk about control not mentioning the neuroendocrine system with the task to maintain the glucose homeostasis of the human body, against changes generated by internal and external agents. In this scenario, the hypothalamus as a regulatory organ of the endocrine system manages the production and consumption of energy to use it equally in the distributed integrated system of the human body, in order to not compromise essential functions of this system. In this management, the hypothalamus must ensure correct levels of glucose not only for the organs but also for the proper functioning of the brain since glucose is the primary source of energy for the proper functioning of the brain.

Therefore, when we talk about a control system, we are referring to the hypothalamus with its complex circuits of sensor neurons, coupled to the pancreas via the hypothalamus—pancreas and the HPA axes.

The correct functioning of the hypothalamic glucose control depends on two dedicated types of neurons, namely the "Glucose—Excited neurons (GE)" and the "Glucose—Inhibited (GI) neurons", they control the rise and fall of blood glucose circulation, these neurons sense any severe energy deficit (fasting, for instance) that supposedly puts the brain at risk and do respond immediately to that imminent risk, and thus maintain the euglycemia.

During an energy deficit in the system, with specific fasting, for example, the hypothalamic glucose-sensing neurons are excited ("informed") of the scenario by the decrease in circulating glucose. So, there is an increase in the activity of these neurons and a gain in relaying information about the availability of glucose in the system and a greater prioritization of glucose supply to the brain. Pathologies also cause changes in glucose sensitivity which can also cause an overload in the functions of these neurons causing possible noticeable dysfunctions, if persistent.

In order to ensure this integrated and coupled control, as already mentioned the hypothalamus has highly specialized glucose-sensing neurons distributed throughout the nucleus, thus enabling the control of distinct neuroendocrine functions. These neurons play a key role in ensuring that the hypothalamus correctly and accurately distributes glucose/energy between organs to keep the body functioning properly, without jeopardizing the brain's glucose supply. Dysfunctions in the underlying mechanisms of glucose detection in neurons within the hypothalamic nucleus will certainly cause hypoglycemia or hyperglycemia and if not treated correctly can lead to death (in severe hypoglycemia) or T1DM.

The aim here is to emphasize this role and the importance of sensor neurons in the hypothalamic control of endocrine function and the consequent implications for hyperglycemia and diabetes mellitus in the case of systemic dysfunctions.

To fully understand the role of the glucose central control on the onset of persistent hyperglycemia and pancreas overload, it is necessary to understand the dynamics of the hypothalamus coupling to the CNS and the behavior of its sensor neuron circuits under external and internal stressors conditions.

As far as the HPA axis is concerned, it is also important to mention the role of the adrenal norepinephrine which likes the epinephrine (Adrenaline) also increases the heartbeat and the blood sugar level. Glucagon and catecholamines (norepinephrine and dopamine) stimulate also net hepatic glucose flux by increasing the hepatic glucose production mediated by glycogenolysis and gluconeogenesis. As might well be learned from the references that follow, hyperglycemia can continue due to the mediation of epinephrine on gluconeogenesis and glucose disposal persists once adrenaline triggers the body's fight-or-flight response. Norepinephrine is, as well known, related to stress, both epinephrine and norepinephrine increase blood sugar level, and both can connect the strain-stress to body sugar levels. Note that stress refers to the load applied to pancreas, while a strain is a deformation or change in the functioning of the pancreas that results from the applied.

3. Disfunctions in Glucose Sensing Neurons Circuit System and Pancreas Exhaustion

Here, we will look for situations where the hypothalamus can be dysfunctional under external and/or internal noxious stressors and the possible consequences of it.

As well known, the glucose-sensing neurons are located in different regions of the hypothalamus (among other brain areas), and studies have focused on each of these regions separately. Therefore, there are not many experimental studies on all regions. There are around twenty-six experimental studies that performed stimuli on these neurons to assess the impact of this stimulus on blood glucose, as can be seen, for instance in the two samples of references below (see also references therein):

Remote control of glucose-sensing neurons to analyze glucose metabolism, Alexandra Alvarsson and Sarah A. Stanley, Am J Physiol Endocrinol Metab. 2018 Sep 1; 315(3): E327-E339.

Central Mechanisms of Glucose Sensing and Counterregulation in Defense of Hypoglycemia, Sarah Stanley, Amir Moheet,[2] and Elizabeth R Seaquist, Endocr Rev. 2019 Jun; 40(3): 768-788. (PMID: 30689785)

As mentioned in Section II, the hypothalamus plays a fundamental role in modulating pancreatic secretions. The electrical stimulation of the ventromedial anterior hypothalamus increases pancreas secretions, and the posterior hypothalamus decreases pancreatic secretions. Therefore, it is important to understand that the pancreas is an important endocrine hormone source, but it is the hypothalamus that is the key central control of glucose homeostasis.

To understand how the strain-stress overloads the pancreas driving it to dys-

functions cannot be only considering the pancreas by itself as the main source of the problem. One must consider also the role played by hypothalamus in this dysfunction scenario, we consider not coupling the dysfunctional system to the hypothalamus dynamics misleading. Dysfunctions in the hypothalamus will affect pancreas and glucose homeostasis directly, and so the euglycemia, inducing persistent hyperglycemia and diabetes mellitus [21].

Furthermore, brain/hypothalamus in many situations works under strain-stress, disease, and dysfunctional conditions. Hypothalamic factors are coupled to the regulation of the pancreas via the hypothalamus-pancreatic axis and indirectly via the HPA axis. And so, pancreas can indeed work overloaded, under strain-stress, and disease, and so can present dysfunctions, now clearly not necessarily related to the immune system, that will affect directly the glucose homeostasis and the euglycemia [22] [23].

To ensure normal body function, the human body depends on tight control of its blood glucose levels, and so hypothalamus-pancreas axis dysfunctions of any nature are very harmful to homeostasis and euglycemia. The scenario is even more complicated since the glucose homeostasis to achieve euglycemia is only possible to be reached if a sophisticated and highly nonlinear network of hormones and neuropeptides released mainly from the brain, pancreas, liver, and intestine works properly. Other parts of body also take part in this marvelous complex network and signaling pathways underlying the complete network. With no caveat, the key players here are the hypothalamus and the pancreas which contributes to sugar-lowering and sugar-increasing with insulin and the counter hormone glucagon.

In this way, dysfunctions in the interaction of the hormones and peptides may lead to disorders such as mellitus diabetes.

Therefore, it is of paramount importance to access and understand the mechanisms underlying the various related dysfunctions of the hypothalamus-pancreas axis and the consequent stress and overload of both endocrine organs [24]. And so, we can ensure that the brain/hypothalamus directly affects the pancreas, by modulating pancreatic insulin and glucagon secretions via the parasympathetic and sympathetic efferent nerves that innervate pancreatic α- and β-cells [25].

Of course, the pancreas, with endocrine and exocrine functions producing enzymes and specialized hormones to control a variety of body functions, can be affected by several diseases such as an enlarged pancreas, genetic disorders and certain autoimmune disorders which lead to diseases such as pancreatitis or inflammation of the pancreas, however in many situations the cause is unknown, and it is called idiopathic pancreatitis that can eventually lead to permanent pancreas damage. And so, if the insulin-producing cells in the pancreas are damaged by stress, inflammation, overload, or autoimmune disorders, diabetes mellitus may appear.

The relevant question here is to find which precursors/stressors are involved

in pancreas overload, stress up to exhaustion, dysfunction, and disease. Also, which role the hypothalamus plays in this scenario? [26].

The importance of defining the real causes for dysfunctions in glucose homeostasis is related to the possibility that the homeostatic control is causing the pancreas to stress, overload, and dysfunctional where in this case the pancreas can be triggered to regenerate itself, as shown in literature, thus restoring the function of the organ and so the euglycemia, what is not possible when pancreas beta cells are destroyed [27] [28] [29].

In addition to the overloading artificial causes, the pancreas has also to work continuously harder due to natural aging process and this due to the clear relationship between aging and hypothalamic general function affecting the proper control of glycemia. Also, chronic stress can stress and strain brain and pancreas, these harmful strains will exhaust and induce dysfunctions in these organs. Medications may also reduce pancreatic function and overload. There are a variety of situations overtaxing the pancreas and inducing diseases such as diabetes mellitus [28] [29] [30] [31].

Closing this section, we can mention that it is possible to perceive the persistent hyperglycemia driving the body to T1DM via two mechanisms, the first, the conventional view perceives an autoimmune disease characterized by autoreactive T cell-mediated destruction of insulin-producing pancreatic beta-cells, where the loss of beta-cells leads to insulin insufficiency and severe persistent hyperglycemia, with patients eventually requiring lifelong insulin therapy to maintain normal glycemic control [1] [32] [33] [34]. On the other hand, there is also a possible second alternative view of the problem proposed here that should work for many cases of misdiagnosed T1DM and also for cases of idiopathic diabetes. This alternative view requires approaching the problem via possible dysfunctions of the homeostatic hypothalamus central glucose control system that would affect the pancreas with spurious information, inducing overload, and exhaustion. The connection pancreas-hypothalamus is via the hypothalamus-pancreas and HPA axes, where in this scenario the sensor neurons play a fundamental role, and the hole central nerve system [1].

Note that Claude Bernard (French physiologist), as later as mid of the 19th century (1849), called attention to show that the brain could play a key role in glucose regulation. He induced a lesion in the floor of the third ventricle in dogs led to altered systemic glucose levels, and so the role of the central nerve system in the body glucose homeostasis dynamics was considered relevant, showing that it is possible to induce artificial diabetes just by puncturing certain brain region, the produced hyperglycemia remained for a few days. As already known, he named this procedure "*piqûre diabétique*" and linked for the first time glucose homeostasis and the brain to the pathogenesis of diabetes [35]. However, as described by Martin H Lundqvist *et al.*, the finding was later overshadowed by the isolation of pancreatic hormones in the 20th century. Since then, the understanding of glucose homeostasis and pathology has primarily evolved around peripheral mechanism, and the mitigation of its persistent deviation mainly via

insulin intake. In this scenario, the peripheral metabolic tissues include the liver, muscle, and adipose tissue. Thus, the standard view of Diabetes mellitus is to consider it as a group of metabolic diseases involving carbohydrate, lipid, and protein metabolism. It is characterized by persistent hyperglycemia which results from defects in insulin secretion [2] [35]. However, more recent studies and better imaging equipment permit much better details of the neuroanatomic mapping of the central nerve system related to glucose homeostasis and the key neuronal circuits and the related intracellular pathways. Furthermore, the new neuroimaging techniques enable neuroendocrinologists the develop neuroimaging techniques to observe and measure changes of activity in specific central nerve system regions under different metabolic challenges induced by modern life dynamics [35] [36].

In addition, in the scenario of non-insulin-dependent diabetes, we might cote D. A. Pyke [34] [37]:

"The Cause of Non-lnsulin Dependent Diabetes: A Hypothesis My suggestion is that as far as non-insulin dependent diabetes is concerned Claude Bernard was right; this condition is not the result of pancreatic islet failure but of a genetically determined alteration of sensitivity to endogenous neuropeptides acting via the sympathetic nervous system and adrenal medulla to affect hepatic glucose output and insulin release. This suggested mechanism for the causation of non-insulin dependent diabetes may be wrong, but it can be put to the test…"

And so, it is not absurd to assume that persistent hyperglycemia and diabetes mellitus can also have precursors in brain, mainly induced by noxious dysfunctions of hypothalamus sensor neurons circuits, induced by internal and/or external triggers such as electromagnetic fields and stress, causing pancreas overload, stress-strain, and exhaustion, and so persistent hyperglycemia [38]-[54].

4. Conclusions

T1DM is a severe health problem worldwide that affects mainly children and must be properly assessed by the health authorities.

The main medical/clinical model in use today to assess the onset and control of T1DM is based on the destruction of beta cells by the body's immune system, and so no insulin production is available, and it must be supplied externally.

The defectiveness of the current model is that it does not take into consideration the role played by the central glucose control system-glucose sensing neurons circuit system hosted by the hypothalamus. Also, it does not take into consideration, to model/assess the children's hyperglycemia, the effects of external noxious elements, such as the children's daily severe exposure to electromagnetic fields, pollution, and social media-hyperintense cognitive activities by age.

Therefore, it is in order that a new paradigm to assess the T1DM dynamic must be considered for clinical and research purposes, and this new paradigm must take into consideration those new aspects raised in this paper, as shown clearly by the list of references below and references therein.

In addition to the overloading artificial causes above described, the pancreas

has also to work continuously harder due to the natural aging process and this due to the clear relationship between aging and hypothalamic general functioning affecting its proper control of glycemia, but this would affect more the onset of T2DM, rather than type 1 mellitus diabetes type 1 diabetes most often occurs in children but can occur at any age.

To close, it might be useful here to "hear" what Claude Bernard said.

"I do not claim to believe that we have yet reached a complete understanding of diabetes; we have on the contrary seen that we know less about it than we thought we knew" [34].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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