Diabetes and Cartesian Dualism: what is the evidence for a brain-centred gluco-regulatory system?

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Ever since Claude Bernard inserted a knitting needle into the brain of a cat in 1854 there has been an interest in the part that the brain has to play in diabetes. The renowned physiologist discovered that by puncturing the floor of the fourth cerebral ventricle of laboratory animals they developed diabetes mellitus (‘pique diabétique’), thus linking glucose homeostasis and the brain to the pathogenesis of diabetes.1

The discovery of insulin in 1921 rather spoilt this line of research, and scientists and clinicians subsequently became overly focused on defective insulin secretion and action, meaning that the pancreatic islet cell overshadowed the brain as the centre of our understanding of diabetes and the target for therapeutic intervention. The problem with this approach is that it serves to control rather than cure the disease.2

Insulin-independent mechanisms account for approximately 50% of overall glucose disposal, but we know very little about them. Sometimes described as ‘glucose effectiveness’, there is a growing research body which suggests that the brain is in control of dynamically regulating the process of glucose control in order to improve and normalise dysglycaemia. Indeed, defects in such mechanisms are postulated as contributory causes to the emergence of diabetes, an example of which was outlined in a recent leader in this journal ‘Type 3 Diabetes’ on the relationship between Alzheimer’s and diabetes.3 What then is the evidence for a brain-centred gluco-regulatory system (BCGS)?

**Thinking about diabetes**

There is a growing research literature establishing the role of the brain in glucose homeostasis. This can be as a direct effect of insulin action – injection of insulin into discrete hypothalamic areas can lower blood glucose levels and increase liver insulin sensitivity,4 and this has been confirmed by deletion of hypothalamic insulin receptors causing glucose intolerance and systemic insulin resistance.5 On the other hand, it has recently become clear that there are insulin-independent mechanisms through which the brain influences glycaemic control. For example, there have been several animal models demonstrating the effects of leptin acting centrally to normalise blood glucose even in the context of severe insulin deficiency. Leptin action in the brain can coordinate several complex and connected processes between different tissue types to lower blood glucose despite the absence of insulin signalling.6,7

In clinical practice, physiological leptin infusion can block or attenuate many neuro-endocrine responses induced by insulin deficient diabetes; however, it does not normalise hyperglycaemia. If exogenous leptin can activate the BCGS why is this the case? The likely answer is that there is an extensive overlap between the peripheral and central gluco-regulatory mechanisms. Insulin deficiency has marked effects on adipose tissue and thus its ability to secrete leptin. It is therefore believed that insulin deficiency leads to leptin deficiency and failure to trigger the BCGS as neither insulin nor leptin are able to work on the brain.

Other hormones, such as FGF-19 (fibroblast growth factor), a gut hormone which is secreted in response to meals, have been shown to act in the brain to promote insulin-independent glucose lowering.8 There are multiple FGF receptor sub-types throughout the cerebral cortex.9 When administered at pharmacological doses it has strong antidiabetic effects. If given to obese rats via an intra-cerebroventricular route, FGF-19 can significantly improve glucose tolerance.

GLP-1 and GIP are both gut hormones as well as neuro-peptides. We know that GLP-1 therapy works partly by enhancing insulin secretion, but it also works to improve glucose tolerance through mechanisms of insulin-independent action that are incompletely understood. Several studies have shown how GLP-1 can have central effects other than those relating to blood glucose, such as appetite suppression and improvements in mood and quality of life factors.10 GLP-1 action in the hypothalamic accurate nucleus improves glucose tolerance through centrally-acting mechanisms similar to leptin and FGF-19.

A further example of how signalling mechanisms between the gut and the brain are crucial to our understanding of diabetes comes from the dramatic improvements in glycaemic control which occur following bariatric surgery even before significant weight loss occurs.

Mechanisms underlying the metabolic benefits of bariatric surgery are not fully understood but may involve improvements in both the BCGS and islet cell function. One previous study of diabetic rats undergoing bariatric surgery (duodenal exclusion) showed insulin-independent activation of a neural circuit that inhibits hepatic glucose production (HGP).11 More recent work suggests that insulin signalling is required in the ventromedial hypothalamus for the effect of bariatric surgery to inhibit HGP in obese rats.12,13 There is increasing evidence to suggest that there are strong links between enhanced secretion of FGF-19, the central nervous system and the gut. The potential is therefore to identify how bariatric procedures interfere with the BCGS and perhaps induce diabetes remission through this pathway (without having to resort to surgery).

**Fundamental interconnectedness**

It is possible that the combined response to rising plasma glucose is a rise in insulin concentration, GLP-1, FGF-19 and leptin which activate the BCGS, which together with the traditional pancreatic islet response,
contribute to glucose disposal. However, if this is the case then why has such a relevant regulatory pathway not been detected previously? The theory is that the gold standard method for assessment of in-vivo glucose control is the euglycaemic-hyperglycaemic clamp, through which insulin sensitivity is assessed as the amount of glucose which needs to be infused to maintain stable plasma concentrations, and this ignores the fact that some of the exogenous glucose could have been taken up by insulin-independent mechanisms.

Criticisms of the BCGS hypothesis are that although brain directed interventions can affect glucose homeostasis this cannot be taken as direct evidence of the brain having a physiological role. It is not clear whether the brain plays a part on a day-to-day basis.

Schwartz et al., from the US and Germany, have thus proposed that diabetes represents a failure of two systems, both the pancreas and the brain. Studies show that the BCGS can compensate effectively for severe insulin deficiency, so the suggestion is that additional failure of the BCGS needs to take place in order for diabetes to occur.14

- Proper BCGS function depends on normal islet function, relying on insulin and other insulin-dependent hormones, e.g. leptin, or defective in type 2 diabetes, e.g. GLP-1.
- Animal models with selective hypothalamic neuronal damage show an impaired ability to respond to regulate glucose and weight leading to the metabolic syndrome.15
- Whether some form of hypothalamic injury is occurring in humans with diabetes is under investigation but there are some early data to support this possibility.16

Summary
It is becoming apparent that glucose homeostasis is not entirely reliant on peripheral mechanisms. Metabolic pathways which are insulin-independent are recognised to play an important part in glucose effectiveness; however, it is unclear as to the extent that the BCGS regulates this. More research work is required to look at to what degree normal blood glucose control depends on a functioning BCGS. In turn, does the aetiology of type 2 diabetes relate to BCGS dysfunction and, in conditions such as Alzheimer’s disease, is the degree of neuronal damage a glucose mediated effect?

Finally, knowledge that hormones such as GLP-1, GIP and FGF-19 act on the brain to improve glucose tolerance and insulin sensitivity opens up new therapeutic opportunities for treatment targets. In the complex, developing field of diabetes we are still not sure of whether the body rules the mind or whether the mind rules the body.

‘And what more am I? I look for aid to the imagination. [But how mistakenly!] I am not that assemblage of limbs we call the human body; I am not a subtle penetrating air distributed throughout all these members; I am not a wind, a fire, a vapor, a breath or anything at all that I can image. I am supposing all these things to be nothing. Yet I find, while so doing, that I am still assured that I am a something.’

– René Descartes. ‘Meditations on First Philosophy: In which the existence of God and the distinction of the soul from the body are demonstrated.’

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Declaration of interests
There are no conflicts of interest declared.

References

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