Diabetologia (2009) 52:779–780
DOI 10.1007/s00125-009-1310-2

FOR DEBATE

Glucose allostasis: Disrobing common wisdom

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Received: 2 February 2009 / Accepted: 5 February 2009 / Published online: 6 March 2009

Keywords Allostasis · Disposition index · Insulin sensitivity · Insulin secretion

In their article [1], Wilkin and Metcalf challenge the concept that chronic insulin resistance must be accompanied by an increase in glycaemia even in the presence of normal beta cell function [2]. In close analogy to stress models suggested by Sterling and Eyer [3] and, later, McEwen [4], we named this concept 'glucose allostasis'. In our original paper [2], the term allostasis, which means 'stability through change', was used for two major reasons. First, based on an understanding of the feedback loop between plasma glucose concentrations and insulin secretion, it was considered impossible for the plasma glucose concentration to return to pre-insulin resistance concentrations, since this would remove the major stimulus for the increased insulin secretion that prevents marked increases in glycaemia with worsening insulin action. Second, this conceptual framework was evidenced by data. In Pima Indians with normal glucose tolerance, changes in insulin sensitivity were accompanied by changes in glycaemia. In the proposed model, we defined allostatic load as the detrimental effects of this elevation of plasma glucose concentration.

Wilkin and Metcalf agree with the concept that in an error-actuated null device the error (here, glucose) can never be zero because loop gain can never be infinite. We do not seem to diverge too far from their views in challenging the generally held wisdom that 'normal' beta cell compensation means that the glucose level is kept constant irrespective of the degree of insulin resistance. We agree that this non-zero error may be small, especially under circumstances where the deviation along the hyperbola (the relationship between insulin secretion vs insulin action) is small and the assessment of what is 'normal' beta cell function problematic.

They do, however, disagree with our view that glucose allostasis occurs in vivo in humans and that the allostatic load has detrimental consequences. We believe that three important points were not appreciated. First, Wilkin and Metcalf appear to have missed the point that we were only studying and discussing individuals with normal glucose tolerance [2], people with normal regulation by anyone's standard (and clearly normal by the WHO definition of the glycaemic excursion in response to oral glucose [5]). The model has nothing to do with the failing beta cell or 'homeostatic breakdown' that would occur later in the progression from normal glucose tolerance to diabetes.

Second, and more importantly, the fact that the regulated variable (glucose) is itself toxic was not addressed. Let us use an open window in a thermostatically regulated room in a hot climate as an analogy for insulin resistance in an organism: the air conditioning system (beta cell) goes into overdrive to keep the temperature (glucose) down. However, in contrast to the glucose allostasis concept, the marginally increased room temperature (which causes the system to go into overdrive in an attempt to nullify the error) is not likely to damage anything

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else in the room. Of course, the constant overdrive will accelerate the wear and tear on the cooling system. According to the glucose allostasis concept, the regulated variable, glucose, is—unlike room temperature—harmful [6]. To fully appreciate this, it is important to re-emphasise that we are discussing a fully functional system: the heating system/beta cell is in perfect working order, i.e. homeostasis is fully maintained. Yet, an allostatic load in the form of increased glycaemia (which is undoubtedly harmful) exists. And even Wilkin and Metcalf readily admit that 'the error must be greater than zero' [1].

Third, the regulation of insulin sensitivity/beta cell function by glucose is not designed in such a way that the primary perturbation—insulin resistance (let us assume that insulin resistance is a primary event for the sake of this argument, e.g. in an obese person with normal glucose tolerance)—can be undone or removed by improving insulin secretion. This in sharp contrast to situations under typical homeostatic regulation (in which all the usual feedback loops are operative), such as the response to an oral or intravenous glucose load. Here, all the regulatory mechanisms (increase in insulin secretion, increased peripheral glucose uptake, inhibition of endogenous glucose output, etc) ultimately remove/normalise the primary perturbation (increased flux of glucose into the blood stream).

Interestingly, in their article, Wilkin and Metcalf do not question the primary observations that formed the basis for our model. For example, they seem to accept that Pima Indians with normal glucose tolerance, who had a disposition index at ~4.5 years of follow-up that was similar to that at baseline, showed changes in glycaemia as they shifted down or up the hyperbola, with ranges of 4.56–5.22 mmol/l (82–94 mg/dl) and 4.67–6.39 mmol/l (84–115 mg/dl) observed for fasting glucose and 2 h glucose, respectively, in extreme instances (Table 2 and Fig. 3b of [2]). These changes may seem negligible considering the entire range of glycaemia including diabetes, especially when expressed as a difference and in millimoles, but they clearly demonstrate the allostasis model. Wilkin and Metcalf do not offer an alternative explanation for these observations.

The only remaining question, then, seems to be the accuracy of measuring normal beta cell function as estimated by the disposition index. We did this using the best available measures of insulin secretory function and insulin action in vivo and found changes in glucose with insulin resistance despite normal beta cell function. It may be argued that there was an undetectable failure of beta cell function in these adult Pima Indians even though they had normal glucose tolerance. However, in perfectly healthy children the increase in beta cell function that compensates for insulin resistance during puberty is accompanied by an increase in fasting glycaemia [7]. This is a situation as metabolically normal as can be encountered clinically, but we are doubtful that the majority of diabetologists, unlike Dr Wilkin and Dr Metcalf, would have predicted this increase in glycaemia.

These data independently demonstrate that insulin resistance is (and must be) accompanied by increased glycaemia even in normally functioning beta cells.

We wonder where on the hyperbola Dr Wilkin and Dr Metcalf would prefer to sit (assuming that disposition index is exactly the same everywhere): high and left, i.e. insulin resistant with hyperinsulinaemia and mild hyperglycaemia, or low and right, i.e. insulin sensitive with lower glycaemia and insulinaemia. If their answer is 'low and right', then maybe the new clothes are not so 'misconstructed' after all, but, rather, concealed by 'common wisdom'.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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