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FOR DEBATE

Glucose allostasis: Emperor's new clothes?

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Abbreviation
AIR acute insulin response

Homeostasis denotes the tendency of a system to defend itself against perturbation. The system employed—the negative feedback loop—is ubiquitous, in nature and in mankind's emulation of it. The term homeostasis literally means 'maintenance of the same' and implies minimal change in response to load. Recently, the term allostasis has been used in the context of glucose control to distinguish a state of stability, despite impaired control [1]. It has been given a name, an identity and a place in the literature [1–3], but does it have a theoretical basis?

Feedback loops are sometimes referred to as error-actuated null devices. Any difference (error) between output and set-point causes the loop to adjust its disposition so as to minimise (attempt to nullify) the error [4]. Its capacity to do so depends on the joint responses or gains of its two components (the insulin response to glucose of the beta cells, and the glucose response to insulin of the tissues, respectively). Gain is a quantity, and the multiple of the two gains defines loop gain, referred to more often in diabetology as the disposition index. Glucose control is a function of disposition index.

Because a control loop is continuous, tension exists between the islet response to glucose and the tissue response to insulin, which is resolved by an equilibrium to which the loop settles in the fasting state. Graphically, the equilibrium lies at the intersection of the two response curves, and is defined by the corresponding values for insulin and glucose. Indeed, the point of intersection provides the solution to the equations that describe the insulin response to glucose and glucose response to insulin. The equations, simultaneous because the loop is closed and its components interactive, underpin the HOMA model in which, arguing in reverse, paired fasting levels of insulin and glucose are used to infer the gains of the beta cells (insulin reserve) and the tissues (insulin action) [5, 6].

The error can never be zero, because loop gain can never be infinite. Indeed, if ever the error fell to zero, control would be lost. Error actuates the loop and is crucial to maintaining (or constraining) its output, though the loop that best controls blood glucose, by inference, operates with the least error. Error is a continuous variable, and if it can never be zero, it can never be infinite either. All degrees of blood glucose control operate within this paradigm. Healthy beta cells with high functional reserve alongside healthy tissues with high insulin sensitivity afford optimal control with minimal error because loop gain is maximal, and the loop equilibrates to near set-point blood glucose and minimum insulin levels to achieve it. Homeostasis is effective in such circumstances because even small pertur-

The Emperor's new clothes: A tale of misconstruction by Hans Christian Andersen (1805–1875).

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bations in the error are robustly defended. On the other hand, loss of insulin sensitivity through weight gain or loss of beta cells through accelerated apoptosis will reduce the disposition index, the loop will tolerate greater error and the fasting blood glucose will settle to a higher level. If all degrees of glucose control operate within the one paradigm, is allostasis different from homeostasis, or merely part of a continuum? Control can never be perfect and can never be nil. There are only degrees of control, and the concept of glucose allostasis becomes redundant.

Stumvoll and colleagues [1] invoke the term allostasis from Sterling and Eyer [7], who used it to describe the morning rise in blood pressure consequent on assuming the upright position. The purpose of the adjustment in pressure is to maintain perfusion of the brain against gravity. Blood pressure is under tonic stimulation (its control system defends against falls in pressure), whereas blood glucose is under tonic constraint (its control system defends against rises in glucose). The morning rise in blood pressure (with its postulated effect on atherogenesis—the 'allostatic load') is physiological and has nothing in common with the rise in blood glucose associated with insulin resistance, which is pathological. In the former case, the rise results from re-setting, and is achieved by a healthy loop that responds accordingly (hypotension, not hypertension, is the postural response to weakened control). In the latter, hyperglycaemia results from deteriorating control, not a rise in setting (which would lead to a decrease in insulin levels, rather than an increase). The notions that glucose allostasis is 'the price we pay for a chronic adaptive mechanism' [2], and that the hyperglycaemia of insulin resistance is needed 'to guarantee acute homeostatic regulation' [2], rather than being evidence of homeostatic deterioration, seem fanciful.

Stumvoll et al. observe from studies in Pima Indians that glucose concentrations rise as insulin sensitivity falls [1]. Recognising that insulin secretion cannot fully compensate for the loss of sensitivity that entrains it, and that the disposition index should fall as a result, they nevertheless hypothesise that glucose may increase with loss of insulin sensitivity despite normal compensation [1]. They call the new equilibrium allostasis and refer to the higher level of glucose as an allostatic load. The data, they claim, 'clearly challenge the commonly held view that, in subjects with normal glucose tolerance, the compensatory increase in beta cell function in response to insulin resistance maintains glucose constant' [1]. But this is not the commonly held view, it is a view that was rejected by endocrinology more than 30 years ago [8]. Control theory would predict that loss of insulin sensitivity, in reducing loop gain, would permit the system to tolerate a greater error, settle at a lower disposition index, and equilibrate at a higher glucose level.

Stumvoll and colleagues seek to demonstrate from clinical measurements that, as glucose rises with falling insulin sensitivity, the disposition index remains constant. Most would argue that glucose rises when insulin sensitivity falls only because the disposition index falls. Stumvoll's evidence, however, is only as good as their ability to show that the disposition index was, indeed, unchanged. Its measurement was based on the product of glucose clearance (*M* value) using the euglycaemic–hyperinsulinaemic clamp and the acute insulin response (AIR) during IVGTT. While both techniques are widely used, neither is physiological, they are not derived simultaneously and neither is particularly reproducible. In concluding that the disposition index remains constant while blood glucose varies with insulin sensitivity, Stumvoll and colleagues have assumed—but not demonstrated—that the measure they used was sufficient to detect differences in the disposition index that may have refuted the claim. In reality, the measurement of glucose is precise, while the measurement of the disposition index is not. It is possible, likely even, that they could detect small differences in glucose but failed to detect correspondingly small differences in the disposition index. Control loop theory implies that fasting glucose is a function of the disposition index, and that a difference or change in glucose will be associated with (result from) a corresponding deviation in the disposition index. Statistical power is crucial when the argument for allostasis rests on finding no statistically detectable movement in the disposition index over a range of blood glucose concentrations.

A disposition curve plotted from real data across a range of changing insulin sensitivity will not describe a true hyperbola of constant disposition index, but a quasi-hyperbola of progressively falling disposition index skewed by the extent to which falling insulin sensitivity over the sweep of the curve is incompletely compensated by rising insulin release. To ignore the deviation, or to fail to detect it, will give the (false) impression that glucose rises despite beta cell compensation that is apparently sufficient to maintain a constant disposition index—the conundrum to which the term glucose allostasis has been attached.

The issue can be resolved by whether or not the product of the *M* value and AIR (the disposition index), when applied to Stumvoll's study population, has the power to detect a difference in disposition index over the range of blood glucose levels recorded (0.4 mmol/l or 8 mg/dl). If it does not, it does not seem appropriate to contend that the disposition index is unchanged or that allostasis is an entity.

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

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