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The hyperbolic equilibrium between insulin sensitivity and secretion

Giovanni Pacini*

Metabolic Unit, Institute of Biomedical Engineering, National Research Council, Padova, Italy

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Abstract *Aim:* The interrelationship between insulin resistance and beta cell secretion has been qualitatively described by a hyperbolic function and quantitatively by the *disposition index*. The concepts behind these assumptions are however still controversial and this review aims to briefly recall the main aspects of the hyperbolic paradigm in terms of mathematical representation and derived indices, together with the main criticisms of the various features.
Synthesis: The relationship is analyzed in terms of a qualitative curve with respect to a possible physiological mechanism underlying that particular shape. Quantitatively, the disposition index, which derives from the non-linear hyperbola-like curve, provides an integrated figure of glucose tolerance including both insulin sensitivity and secretion. Different types of metabolic tests and different categories of subjects may yield different mathematical relationships between the two processes. However, various formulas for the disposition index can be wrong and the reasons for this are highlighted.
Conclusions: Insulin secretion and insulin sensitivity are related with an inverse, non-linear function that shows the critical importance of the beta cell dysfunction for the development of type 2 diabetes. The disposition index is a mirror of glucose tolerance and may be important for evaluating those factors that (hypothetically) signal to the beta cell the reduction of insulin sensitivity, for development of possible novel treatments that restore the normal relation between the insulin resistance and the pancreatic activity.

Introduction

It is well accepted that the maintenance of good glucose tolerance depends upon the faultless balance between the processes regulating glucose uptake and production and the hormonal and

* ISIB-CNR, Corso Stati Uniti, 4, 35127 Padova, Italy. Tel.: +39 049 829 5750; fax: +39 049 829 5763.
E-mail address: giovanni.pacini@isib.cnr.it

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nervous signals, which control those processes. Although other factors may play important roles in the preservation of normoglycemia, such as the non-insulin-mediated glucose disappearance (mainly in the central nervous system), insulin sensitivity and insulin secretion remain the most studied metabolic mechanisms responsible for modulating glucose tolerance.

Although it has been known for many years, from obesity studies, that increased insulin resistance is associated with an augmented beta cell secretion [1], only a few studies have shown a clear formulation of the interrelationship between the two processes. Bergman and collaborators reported in normal dogs fed high-carbohydrate [2] and then in obese humans [3] that normoglycemia was maintained because the reduction of insulin sensitivity, proper of those altered metabolic conditions was accompanied by an increased release of insulin. For the first time, the concepts of hyperbolic relationship and of disposition factor were introduced in [3].

Only in the last decade have thorough studies been performed to characterize the (mathematical) relationship between insulin sensitivity and secretion, but this matter is still controversial. Some groups provide evidence that the curve representing the relationship insulin sensitivity/secretion is really a hyperbola, while other investigators raise doubts that this particular mathematical function is applicable to all categories of subjects and insulin secretion parameters, although in general everyone accepts the non-linearity. However, the hyperbola concept has currently driven several studies and this review briefly recalls the main aspects of the hyperbolic paradigm in terms of mathematical representation and derived indices, together with the main criticisms of the various features.

The hyperbolic archetype

The curve

Plotting beta cell function against insulin sensitivity in various categories of subjects had already yielded evidence of a non-linear relationship (e.g., [4]), when Kahn and collaborators showed in a quite large number of subjects that the relationship between the insulin sensitivity index (S_I), calculated with the minimal model of glucose disappearance [5] from frequently sampled intravenous glucose tolerance test (FSIGT) data and a measure of insulin secretion was of hyperbolic nature [6]. Beta cell secretion was estimated from the same tests as the acute insulin response: i.e., the mean incremental (suprabasal) concentration immediately following the glucose bolus, usually between 2 and 10 min (AIR_G). They showed that the non-linearity was represented by a power function $AIR_G = \text{constant} \times S_I^{-\alpha}$; since α resulted not different from 1, they affirmed that the curve was a ''rectangular hyperbola''. Afterwards the non-linearity was demonstrated in several other categories of subjects and with parameters arising from other tests: for instance, in healthy volunteers with insulin sensitivity assessed by the glucose clamp (M/I, where M is the glucose infusion rate and I is steady state insulin concentration) and insulin secretion through the arginine test [7]. Also in this case a hyperbolic relationship was the proper fit of the data.

This asymptotic curve, regardless of whether it is a hyperbola or a generic power function, describes the physiological process that preserves a constant glucose uptake even in the presence of an elevated insulin release. In this situation the body responds by reducing insulin sensitivity. This reduction however after a certain threshold yields a very low value of sensitivity, almost undetectable, despite an even excessive increase of the secretion. Liver and insulin-dependent tissues continue therefore to take up glucose at a sort of constant degree, after insulin secretion exceeds a limit value, proper of every single individual. This type of non-linear curve thus well fits with the representation of biological processes, especially enzymatic reactions, characterized by thresholds and saturation.

The index

The hyperbola hypothesis implies that the product beta cell function $\times$ insulin sensitivity is nearly constant and the constant product $DI = AIR_G \times S_I$ was termed the ''disposition index'' [3,6]. Ever since, this index has been increasingly used in metabolic studies. The importance of DI has been ascribed to the fact that it represents an integrated figure of glucose tolerance, since it accounts at the same time for the two main factors regulating blood glucose. In other words, the disposition index indicates how insulin secretion adapts itself to changes of insulin resistance by modulating the hormone release accordingly [8,9]. Therefore, another interpretation of the disposition index is that it represents an index of beta cell function weighted by ambient insulin sensitivity [10]. Once the DI of a normal population has been