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PERSPECTIVE

Explanation of the Insulin Paradox From the Evolutionary Point of View

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It has been well established that insulin resistance is associated with metabolic syndrome or diabetes resulting in higher mortality.[1–6] However, recently increasing evidence has shown that blocking insulin action results in greater longevity in various life forms such as yeast, *Caenorhabditis elegans*, *Drosophila,* and vertebrate including primates.[1,2,7] Therefore, it appears that the insulin paradox exists.

There are several possible explanations for the insulin paradox from an evolutionary point of view.

First, in general, there are two types of selection in evolution, K-selection and r-selection.[3,8–11] The former of these acts to promote survival, whereas the latter acts to enhance reproduction (Fig. 1). In the benign environment, r-selection may predominate to shift the animal to investment in its reproduction, but in the stressful environment, K-selection may predominate causing the shift toward investment for maintaining the somatic cells of animal, that is, for maintaining its survival (Fig. 2). In evolution, insulin is thought to be a neurohormone in the brain, regulating both metabolism and growth. After the two cycles of whole genome duplications, vertebrates have emerged, which use glucose directly without changing trehalose into glucose as insects do[1] (Fig. 3). Insulin is thought to have concomitantly descended down from the brain to the pancreas in order to regulate blood glucose levels. On the other hand, components of the insulin signaling system, such as insulin receptor, insulin receptor substrate (IRS), and phosphatidylinositol3′-kinase (PI3-K), remained in the brain, especially in the hypothalamus, regulating growth,[1,12] although it is unknown whether the hypothalamic insulin system may interact with the GHRH (growth hormone-releasing hormone)-GH (growth hormone)-IGF (insulin-like growth factor) system. Therefore, the action of insulin to regulate development, growth, or reproduction is more ancient that its action to regulate blood glucose levels[1]. In addition, incretin hormones such as glucagon-like peptide 1(GLP-1) or glucose-dependent insulinotropic peptide (GIP) have attained their ability to stimulate insulin from pancreatic beta cells as a fine-tuning mechanism of blood glucose levels.[1,13] In ancient times, insulin may have acted to shift the usage of metabolic resources from survival to growth or reproduction, that is, a change in selection from K-selection to r-selection.[2] Therefore, insulin resistance may have some advantage in a poor environment by shifting metabolic resources from growth or reproduction to survival.

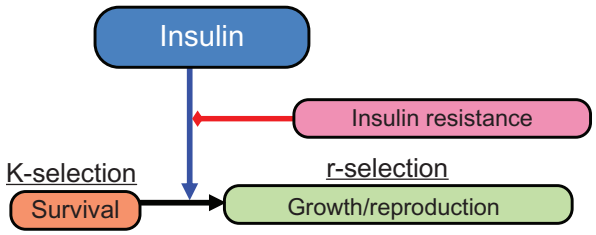

Figure 1. Insulin and shift between survival and growth or reproduction.

Second, insulin resistance in a tissue such as skeletal muscle allows the body to shift its priorities of glucose allocation away from the peripheral tissues and toward the fragile and energy-demanding brain[10] (Fig. 4). During states associated with negative energy balance, such as starvation, infection, or trauma, insulin resistance is triggered, and free fatty acids (FFA) are mobilized from adipose tissue, which induce insulin resistance in the liver and muscle. Adipose tissue also secretes proinflammatory cytokines, further causing insulin resistance in the liver.[10] These mechanisms may help to spare glucose for the brain in a poor environment.

In summary, in ancient times at least, insulin resistance may have had some advantage from an evolutionary perspective. In this context, insulin resistance is one of the mismatches between environmental and evolutionary changes.[1,2–4,14]

Author Contributions

Conceived and designed the experiments: HK. Analysed the data: HK. Wrote the first draft of the manuscript: HK. Contributed to the writing of the manuscript: HK. Agree with manuscript results and conclusions: HK. Jointly developed the structure and arguments for the paper: HK. Made critical revisions and approved final version: HK. All authors reviewed and approved of the final manuscript.

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Competing Interests

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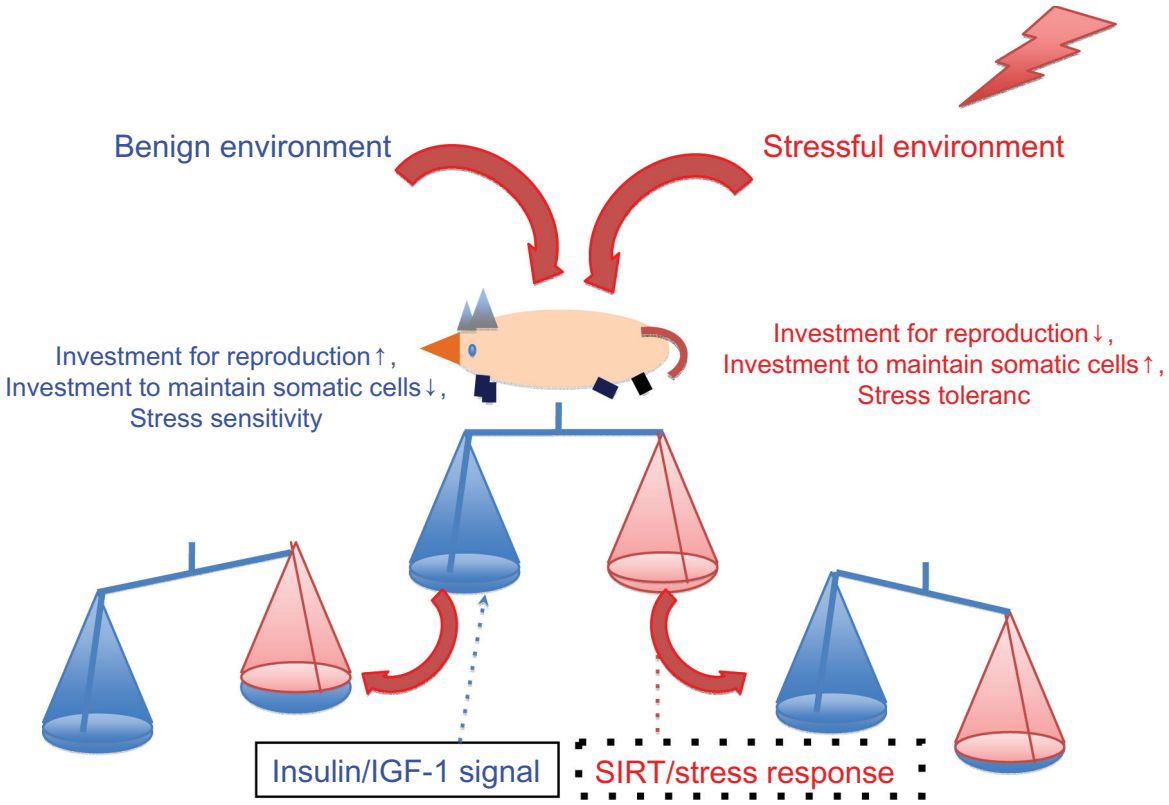

Figure 2. Insulin/IGF-1 signal and SIRT(sirtuin)/stress response depending on the environment state.
From Stearns SC, Koella JC. *Evolution in Health and Disease*. 2nd ed. Oxford University Press; 2008 with modifications.

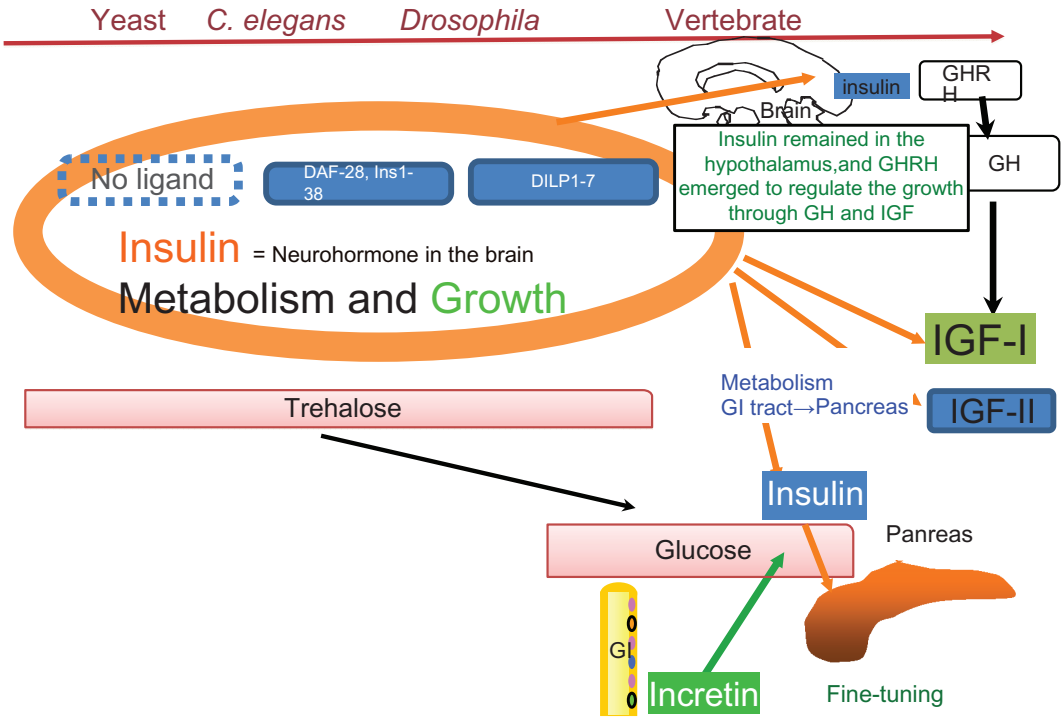

Figure 3. Evolution of insulin signaling system.
Abbreviations: GI, gastrointestinal tract; IGF, insulin-like growth factor.

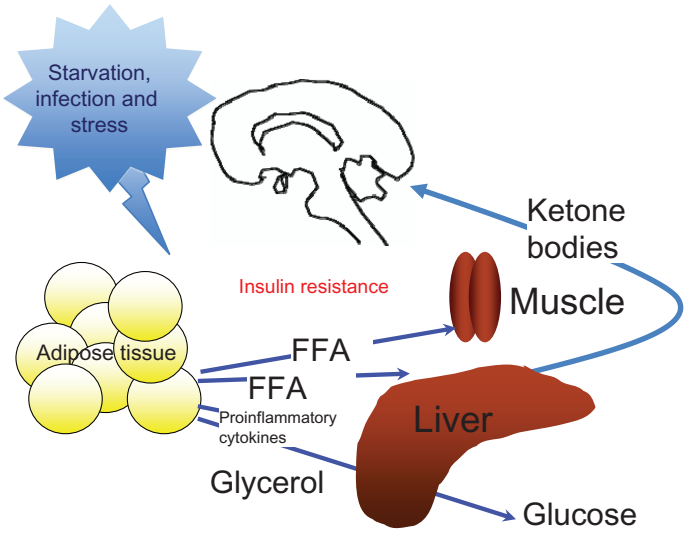

Figure 4. Brain protection hypothesis.
From Muhlenbein MP, editor. *Human Evolutionary Biology*. Cambridge, UK: Cambridge University Press; 2010 with modifications.

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Disclosures and Ethics

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