Hypothesis: Klotho can decouple Insulin resistance from the associated pathophysiology

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Background:
A very fundamental paradox of insulin resistance is that in a wide variety of animal models impairment of insulin signaling increases life span. But in humans it increases the risk of a range of fatal disorders. Insulin resistance giving rise to hyperinsuliemia, beta cell failure and hyperglycemia is believed to be the sequence of events central to T2D. Hyperglycemia is presumed to lead to other pathophysiological effects through vascular inflammation, angiogenesis dysfunction, oxidative stress and EGF deficiency.
The emerging alternative view is that neuro-behavioural changes central to T2D and they independently lead to hyperinsulinemia, vascular inflammation, angiogenesis dysfunction, oxidative stress and EGF deficiency. Insulin resistance develops as a compensatory response to hyperinsulinemia.

Hypothesis:

The pathophysiological mechanisms of T2D are not a direct consequence of hyperglycemia and therefore can be potentially decoupled from it. The Klotho protein mediates the decoupling and therefore suggests a potential change in the paradigm of treatment of T2D. This falsifies the traditional view of the sequence and causal relationships between the pathophysiological mechanisms (fig 1) and suggests a novel view (fig 2).

Figure 1:
Pathophysiology: orthodox view

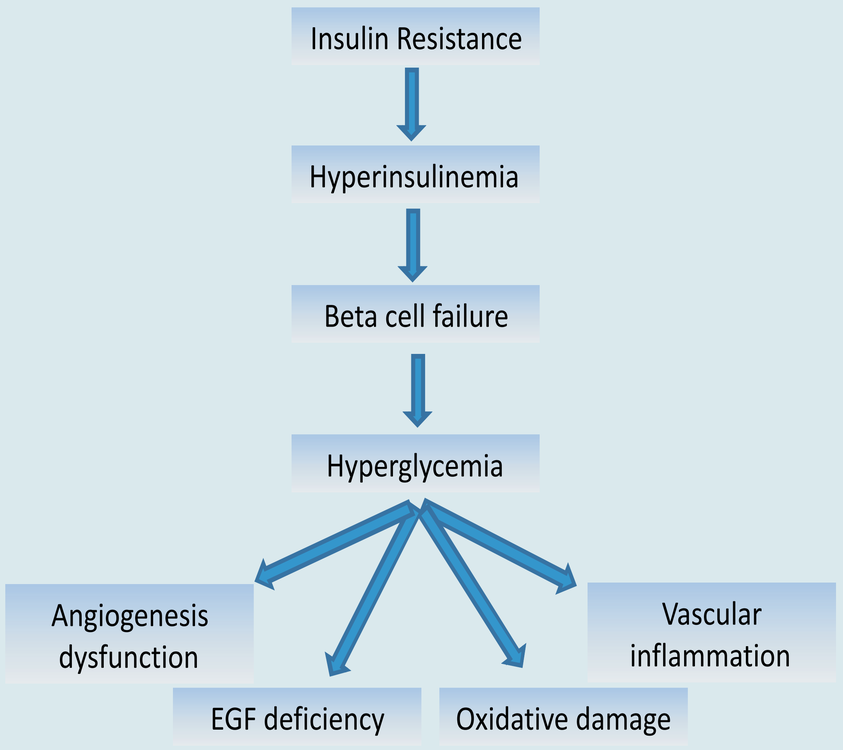
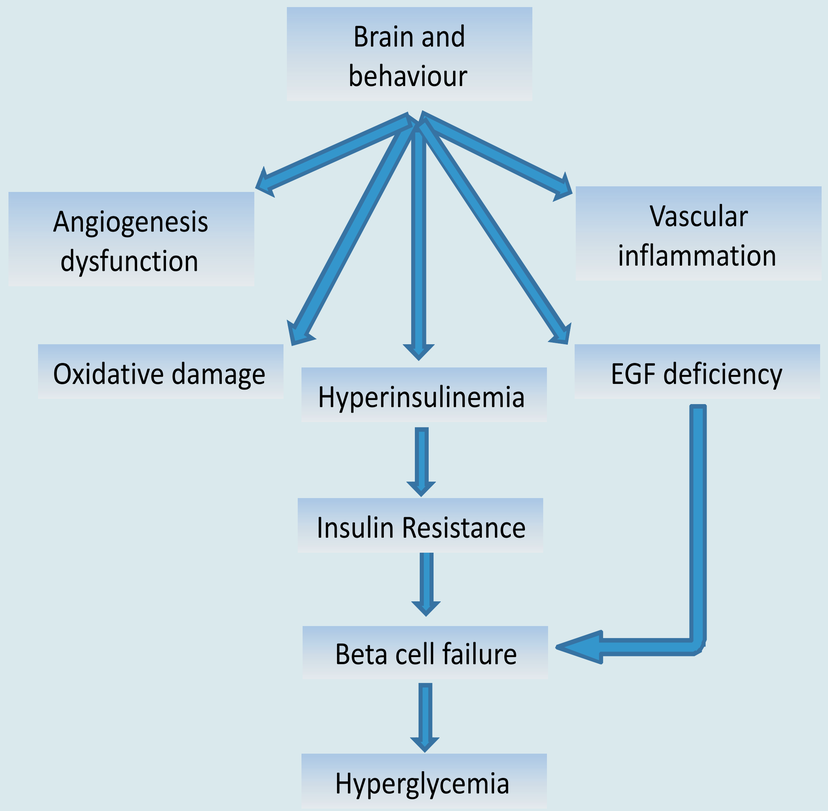


Figure 2:
Pathophysiology: according to the Neurobehavioral origins hypothesis



Support of the hypothesis:

1. Klotho gene overexpression is consistently shown to increase lifespan and Klotho knockouts are early aging phenotypes (1-2).
2. Klotho gene overexpression induces insulin resistance in vivo (3-4). The result is consistent across studies.
3. Klotho protein has proangiogenesis (6), anti-inflammatory (7), anti-oxidant (8) and EGF stimulatory (9) actions.
4. The main mechanisms of diabetic complications are systemic inflammation, angiogenesis dysfunction, oxidative stress and EGF and other growth factor deficiencies (10).Taken together it can be seen that insulin resistance can certainly be decoupled from its pathophysiological correlates.

Conclusions:

1. The Klotho protein can effectively decouple insulin resistance from the other pathophysiological processes and the decoupling supports the new paradigm over the orthodox view.
2. This has important implications for medicine. Rather than targeting insulin resistance the next generation anti-diabetic drugs should target angiogenesis, inflammation, oxidative stress and EGF deficiency.

Insulin resistance by itself may not have any pathological consequences and also may not be causally related to other pathophysiological mechanisms.
The Klotho protein itself may have anti-diabetic action although it may not normalize blood sugar levels.

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