Pathophysiology of Insulin Resistance: Connecting the Dots

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INSULIN RESISTANCE PHYSIOLOGY

This is a compilation of available data on Insulin Resistance (IR) postulating a unifying etiologic hypothesis and a pathophysiologic classification of IR.

BASAL METABOLISM: Fuel Journey from Gut to Mitochondria

- Metabolically inflexible cells, e.g. brain, depend exclusively on glucose oxidation and upon gluconeogenesis during fasting. They have capacity to store glucose as glycogen but no storage of triglycerides (TG).
- Metabolically flexible cells, e.g. myocytes can use either glucose or fatty acids (FFA) or both at a time, for glycolysis & beta-oxidation. They can store both glycogen and TGs.
- The capacity to store glycogen & TGs is genetically inherited.

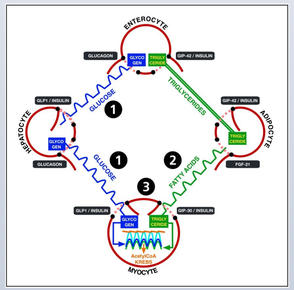
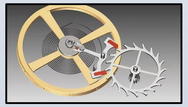


Fig. 1



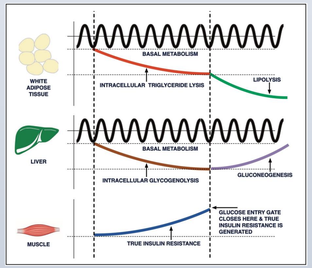
This clock movement illustrates the Flip-Flop mechanism.

- Insulin regulates entry of glucose, while glucagon regulates the exit. (**Insulin-Glucagon flip-flop**, Fig 1.1) This flip-flop mechanism transports glucose from the enterocytes to myocytes, via hepatocytes, in a jerky intermittent flux, akin to an electrical half wave rectifier.
- In the myocytes, the buffering action of intracellular glycogen, converts this intermittent flux of glucose into a smooth forward flux, akin to an electrical full-wave rectifier.
- Similar flip-flop is operated for FFAs, between adipocytes and myocytes, by FGF-21 and insulin. (**Insulin-FGF21 flip-flop**, Fig 1.2)
- Third flip-flop resides on myocyte cell wall, which is operated by the intra-myocytic storages of glycogen and TG & their entry ports. (**GLP1-GIP30 flip-flop**, Fig 1.3) These ports have two levels of opening, Basal & Prandial. When glycogen storage is full, glucose port closes and TG port opens and vice versa. The '**basal Flip-Flop**' works continuously during lifetime and constitutes '**the Metabolic Heart**'.
- Glycogen & TG intracellular storage capacity determines the maximum prandial GLP-1& GIP42 secretion.
- Simultaneous use two fuels doubles the amount of acetylCoA generated, akin to the electrical voltage doubler mechanism.

INCRETINS: THE MASTER CONTROLLERS OF METABOLISM

- GLP-1 is a glucose sensing incretin, whereas GIP(1-42) is a FFA sensing incretin and are secreted in the gut by L & K cells.
- Incretins are insulin secretagogues.
- Alpha cells secrete GLP-1 & a novel incretin, GIP(1-30).
- Alpha cells are the **pacemakers of basal metabolism** oscillations.
- Alpha cells sense hyperglycemia and hypoglycemia to activate either Proprotein convertase (PC) 1/3 or 2 respectively. This results in the differential processing of Proglucagon into either GLP-1 or Glucagon, respectively. Along with Glucagon, PC2 also activates secretion of GIP30, which operates the basal metabolism 'GLP1-GIP30 Flip-Flop' on myocytes coordinating the entry of glucose & FFA. (**Fig 4**)

Fig. 2:
FASTING METABOLISM & GENESIS OF FASTING IR



- During fasting, hepatic glycogen gradually depletes, FFA oxidation increases, muscle glycogen accumulates, closing glucose entry. Low hepatic 'glucose-6-phosphate' stimulates FOXO-1, PPAR-alpha & FGF21 stimulating exoWAT lipolysis and at a later stage, ketogenesis. (FIG.2)

Fig. 3:
PRANDIAL METABOLISM & STORAGE OF FUELS

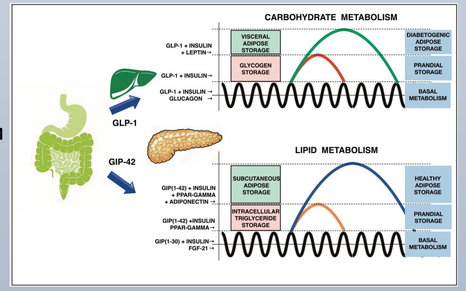
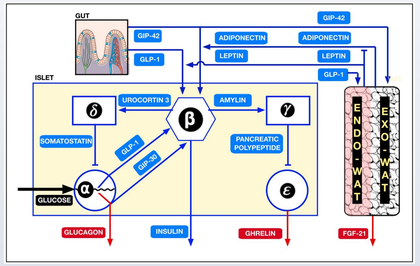


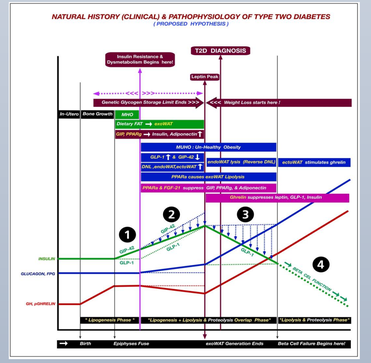
Fig. 4:
HORMONAL CONTROL METABOLISM



PATHOPHYSIOLOGY OF INSULIN RESISTANCE

- The peripheral water-medium based homeostasis is regulated by the islet of pancreas, while the lipid homeostasis by the PPAR system.
- The speed of metabolism for both (water & lipid) media is controlled by hypothalamus via the pituitary hormones, ACTH and TSH, respectively along with the autonomous nervous system.
- After the completion of active growth, surplus energy intake is stored as fat and is used during the fasting state.
- Dietary carbohydrates & fats are first stored as glycogen & TGs intracellularly in liver, adipose tissue and muscles. This storage capacity is genetically inherited and is the basis of '**Genetically Inherited IR**'.
- Excess dietary fats are stored as subcutaneous fat (**exoWAT**) via 'GIP42-coupled-Insulin', promoting proportionate secretion of Adiponectin & '**Euglycemic Hyperinsulinemia**'. This results in 'increased fasting insulin / normal fasting glucose' ratio, (**Mathematical IR**) (Fig5.1).
- This stage represents metabolically Healthy Obesity (MHO).

Fig. 5:
TRAJECTORY OF IR STAGES & EVOLUTION OF T2D



PATHOPHYSIOLOGY OF INSULIN RESISTANCE Contd.

- Surplus carbohydrates trigger de-novo-lipogenesis (**DNL**) in liver and adipose tissues. (FIG.3) The generated TGs (**endoWAT**) share space with exoWAT by promoting the lipolysis of equal amount of exoWAT.
- The endoWAT secretes proportionate amounts of Leptin, a GLP-1 secretagogue. (Fig 5.2) Leptin stimulates proportionate GLP-1 and inhibits PPAR-gamma by phosphorylating it at its serine-273 residue. This stimulates equivalent amounts of PPAR-alpha causing exoWAT lipolysis, thus increasing FFA flux.
- FFA flux proportionately increases intracellular glycogen, in all tissue cells, except those cells, which are capable of gluconeogenesis. FFA flux also causes TG accumulation in metabolically flexible cells
- Thus, FFA flux generates universal '**Tissue IR**'. (Fig 5.2).
- Tissue IR counterbalances & negates the hyperinsulinemia of GIP42 by 'hyperinsulinemia caused by GLP-1' and simultaneously generates hyperglycemia & hyperFFA-mia. This marks the beginning of dysmetabolism and Metabolically Unhealthy Obesity. (MUHO)
- This stage is associated with increased glycolysis, endothelial dysfunction, vascular IR and cardiovascular morbidity. (Fig 5.2)
- Next stage begins after saturating intracellular glycogen & TG storages and reaching the maximum Tissue IR/Leptin-Peak. Continued carbohydrate excess stimulates ghrelin secretion and lipolysis of endoWAT (**Reverse DNL**) (Fig 5.3) T2D diagnosis is manifests early in this stage. This stage ends as the endoWAT lipolysis completes.
- During next stage (Fig 5.4) basal metabolism is involved, as ghrelin and FGF21 continue to suppress incretins/insulin. Hypoinsulinemia develops and reduces the intensity of metabolism, causing cellular starvation. This stage resembles T1D.

PATHOPHYSIOLOGIC CLASSIFICATION OF 'IR'

- **Hereditary IR (Monogenic / Polygenic)**
  - **Hepatic (Fasting hyperglycemia)**
  - **Muscular (Obese T2D)**
  - **Adipose (Lean T2D)**
- **Fasting induced IR (Physiological, with normal incretins)**
- **Mathematical IR (Metabolically neutral)**
- **Tissue IR (Dysmetabolism & T2D)**
  - **Vascular, Hepatic, Muscular, Adipose, Brain, Renal, Intestinal, Gonadal, etc.**

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