Pathophysiology of Insulin Resistance: Connecting the Dots

Dr. Suresh N. Shinde, MD.

Poona Hospital and research Center, Pune, INDIA ; Academy of Continuing Medical Education & Research, Pune, INDIA ; Aloha Lifestyle Reversal Studio, Pune, INDIA

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CONTACT:
acmepune@yahoo.com

SCAN ME

BRIEF OVERVIEW

This is a compilation of available data on Insulin Resistance (IR) postulating a unifying etiologic hypothesis, a pathophysiologic classification of IR and a proposed timeline of obesity, incretins, & unique stages of evolution of T2D

PROPOSED PATHOPHYSIOLOGIC CLASSIFICATION OF INSULIN RESISTANCE

- 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 with suppressed incretins)
  - Vascular, Hepatic, Muscular, Adipose, Brain, Renal, Intestinal, Gonadal, etc.

INSULIN RESISTANCE PHYSIOLOGY

- 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.

INCRETINS: THE MASTER CONTROLLERS OF METABOLISM

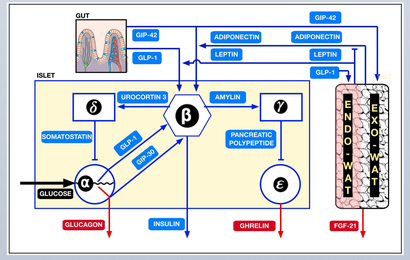


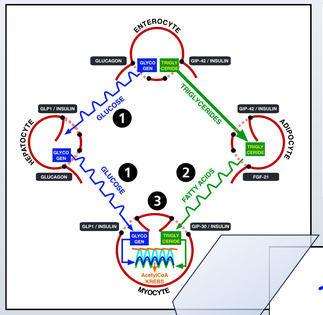
Fig 1: HORMONAL CONTROL OF METABOLISM

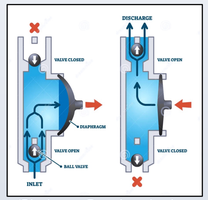
- GLP-1 is a glucose mediated incretin, whereas GIP(1-42) is a FFA mediated incretin and are secreted in the gut by L & K cells.
- Incretins are insulin secretagogues.
- Alpha cells secrete GLP-1 & another novel incretin, i.e. GIP(1-30).
- Alpha cells are the **pacemakers of basal metabolism** oscillations.
- 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 1 & 2**)

PATHOPHYSIOLOGY OF INSULIN RESISTANCE

BASAL METABOLISM: GLUCOSE & FATTY ACIDS

'JOURNEY FROM GUT TO MITOCHONDRIA'





'Diaphragm Pump' mechanism illustrates the 'Flip-Flop' action.

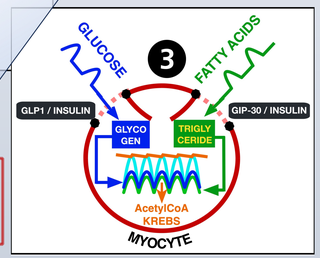


Fig. 2: The journey of fuels from the gut to muscle mitochondria with myocyte events shown in the magnified subset.

- Insulin regulates entry of glucose, while glucagon regulates the exit. (**Insulin-Glucagon flip-flop**, Fig 2.1) 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 2.2)
- 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 2.3, Fig 1) 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 ***an electrical voltage doubler mechanism***.

PATHOPHYSIOLOGY OF INSULIN RESISTANCE

FASTING & EXTENDED FASTING METABOLISM

- During fasting, hepatic glycogen gradually depletes, FFA oxidation increases, muscle glycogen accumulates, closing glucose entry (IR). Low hepatic 'glucose-6-phosphate' stimulates FOXO-1, PPAR-alpha & FGF21 stimulating exoWAT lipolysis and at a later stage, ketogenesis. (FIG.3)

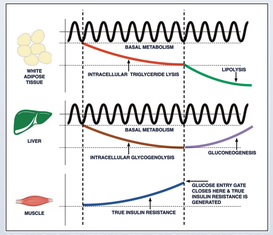


Fig. 3: FASTING & EXTENDED FASTING METABOLISM

PRANDIAL METABOLISM

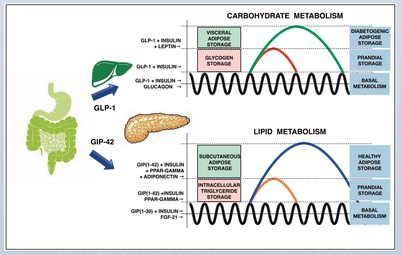


Fig. 4: PRANDIAL METABOLISM & STORAGE OF FUELS

- The peripheral 'water-based homeostasis' is regulated by the islets 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 intracellularly as glycogen & TGs in liver, adipose tissue and muscles. This storage capacity is genetically inherited and forms 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 to normal fasting glucose' ratio, (**Mathematical IR**) (Fig5.1).
- This stage represents Metabolically Healthy Obesity (MHO).

PATHOPHYSIOLOGY OF INSULIN RESISTANCE Contd.

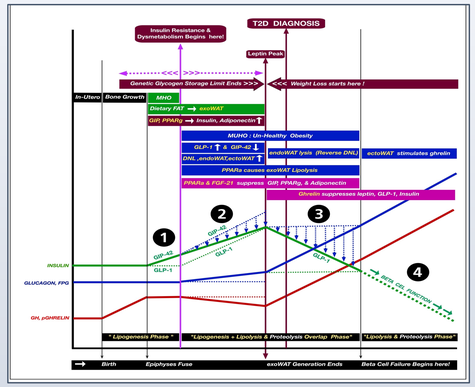


Fig. 5: TRAJECTORY OF IR STAGES & EVOLUTION OF T2D

- Surplus carbohydrates trigger de-novo-lipogenesis (**DNL**) in liver and adipose tissues. (FIG.4) 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 influx leads to proportionate accumulation of glycogen, in all tissue cells, excepting the gluconeogenesis-capable cells. FFA influx also leads to proportionate TG accumulation in metabolically flexible cells
- Thus, FFA influx generates universal '**Tissue IR**'. (Fig 5.2).
- Tissue IR counterbalances & negates the 'exoWAT-GIP42 based hyperinsulinemia' by 'endoWAT-GLP1 based hyperinsulinemia' and simultaneously generates hyperglycemia & hyperFFA-mia. This marks the beginning of dysmetabolism and Metabolically Unhealthy Obesity.
- This stage is associated with 'glycolysis>>gluconeogenesis', endothelial dysfunction, vascular IR and cardiovascular morbidity. (Fig 5.2)
- Next stage, (Fig 5.3) when the intracellular glycogen & TG storages are saturated, and the maximum Tissue IR/Leptin-Peak are reached. Continued carbohydrate excess, stimulates ghrelin secretion and lipolysis of endoWAT (**Reverse DNL**). T2D diagnosis is manifests early in this stage. This stage ends after the completion of the endoWAT lipolysis.
- During the next stage (Fig 5.4), as ghrelin and FGF21 continue to suppress incretins/insulin, basal metabolism slows down. Hypoinsulinemia develops and reduces the intensity of metabolism, causing cellular starvation & apoptosis. This stage resembles T1D.