The exoWAT, endoWAT and ectoWAT Dictate Dysmetabolism, Dyslipidemia & Diabetes

Dr. Suresh N. Shinde, MD,MNAMS,FISE,FICN

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

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BACKGROUND

Standard 75-gram, two-hour OGTT along with insulin levels was used in over 2000 individuals and the data was analysed to determine the evolution of T2D and its relationship to heredity and obesity. Analysis of the temporal patterns of insulin secretion, insulin resistance and disposition indexes, obesity and family history some patterns emerged. These patterns of insulin and glucose kinetics enabled to formulate a hypothesis which tries to explain the occurrence and temporal profile of T2D and its various clinical phenotypes. Three-tier model depicting physiology of metabolism and a timeline of dysmetabolism, dyslipidemia and diabetes is proposed.

THREE TIER MODEL OF METABOLISM

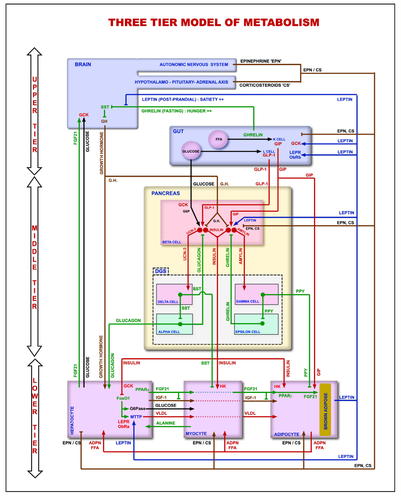


Fig. 1

DISCUSSION

A clinical model is conceptualized to explain the integrated physiology of pancreatic islet, hypothalamus, gut and peripheral tissues regulating the carbohydrate, fat, protein and energy metabolism. (Fig.1)

MIDDLE TIER:

The beta cells regulate anabolism mainly by secreting insulin, urocortin-3 and amylin. Urocortin-3 stimulates delta cells to secrete somatostatin (SST) and amylin stimulates gamma cells to secrete pancreatic polypeptide (PPY). SST inhibits glucagon which controls glucose and protein catabolism. PPY inhibits ghrelin which controls lipid catabolism. Ghrelin and glucagon inhibit beta cells. Thus this **'Delta-Gamma system'** controls catabolism very much like an electronic 'flip-flop' circuit analogous to accelerator and brake of a vehicle.

UPPER TIER:

Brain secretes GH which stimulates hepatic IGF-1 and inhibits fibroblast growth factor 21 (FGF21) as well as the beta cells.

Ghrelin stimulates appetite whereas leptin suppresses it.

ANS and hypothalamo-adrenal axis inhibit gut incretins, beta cells and hepatic anabolism.

The incretins secreted by the gut also stimulate beta cells.

Leptin stimulates beta cells favouring lipogenesis in addition causing satiety by its central action.

LOWER TIER:

Liver secretes IGF-1, FGF21, glucose (gluconeogenesis) and VLDL (De novo lipogenesis, DNL). Liver function is modified by leptin, GH, insulin, glucagon, adiponectin and glucocorticoids.

Muscles are main hub of energy utilization and is acted upon by insulin, SST, glucocorticoids and adiponectin.

The adipose tissue is regulated by insulin, PPY, FGF21, glucocorticoids and GIP. FGF21 converts white adipose tissue (WAT) into thermogenic brown adipose tissue (BAT).

HUMAN BIO-ENERGETICS

It deals with acquiring and storing energy as well as utilising it for life processes. (Fig.2)

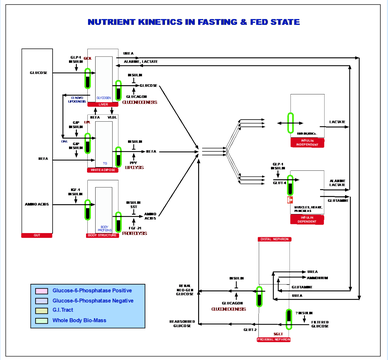


Fig. 2

ENERGY ACQUISITION:

- Gut absorption
- Fats → Chylomicrons – GIP
- Carbs → GLP-1

ENERGY STORAGE:

- Glucose → Glycogen
- Fat (dietary) → **exoWAT**
- Fat (DNL) → **endoWAT**
- Amino acids → Body proteins

ENERGY EXPENDITURE:

- Cellular respiration – muscles, heart etc.
- Brain activity
- BAT thermogenesis
- Glycolysis, lipolysis & proteolysis

ENERGY STORAGE

ROLE OF INSULIN & LEPTIN

WAT generates adiponectin and leptin.

Adiponectin facilitates entry of FFA into muscle and liver.

Leptin has 4 actions.

1. Stimulates insulin secretion by beta cells.
2. Inhibits ghrelin and causes satiety by hypothalamic action.
3. Modifies gut incretin secretion.
4. Stimulates Mitochondrial Triglyceride Transfer Protein (MTTP) in hepatocytes. (Fig.3)

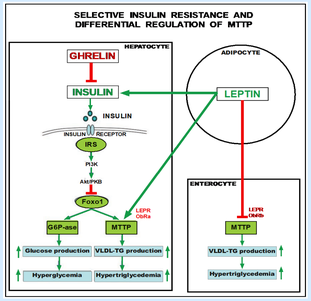


Fig. 3

Insulin is essential for both exoWAT & endoWAT lipogenesis. Adiponectin secretion is proportional to total body WAT, whereas leptin secretion is proportional to total body endoWAT. Leptin has a dual action on hepatocytes. It stimulates insulin secretion which supresses gluconeogenesis & hepatic DNL. However, leptin directly stimulates MTTP & DNL. Leptin also inhibits gut MTTP. This explains the ' Euglycemic Hyperinsulinemia' & the rising levels of fasting leptin as well as insulin with rising endoWAT-associated obesity. This has been normally termed as '**Acquired Insulin Resistance**'

WAT storage capacity (cWAT) is genetically determined. When cWAT is exceeded, fat deposition occurs ectopically in non-adipose tissues as **ectoWAT** and stimulates growth hormone, ghrelin and hyperglycemia. EctoWAT suppresses insulin, stimulates glucagon and ghrelin, leading to hyperglycemia, lipolysis & beta cell suppression-cum-failure. Calorie surplus, superimposed on genetic insulin resistance drives the timeline of dysmetabolism. (Fig.4)

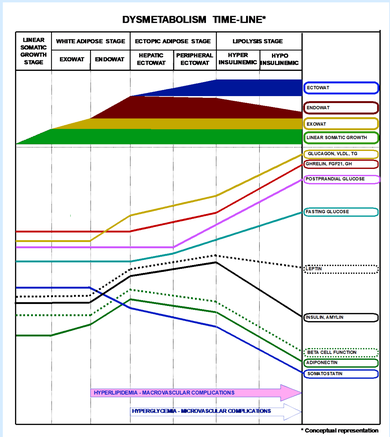


Fig. 4

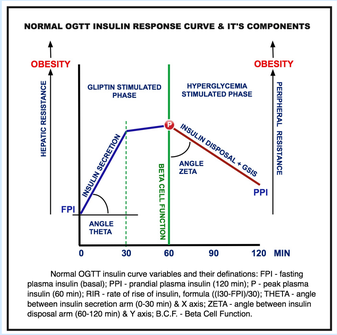
TIMELINE OF DYSMETABOLISM & DYSGLYCEMIA:

- Normal metabolism
- exoWAT → healthy obesity, no dysmetabolism
- endoWAT → unhealthy obesity, dysmetabolism, dyslipidemia, hypertension, macrovascular morbidity, fasting hyperinsulinemia & hyperleptinemia but no dysglycemia
- Hepatic ectoWAT → MAFLD (fatty liver), Fasting glucose, ghrelin & GH rise & BCF suppression begins
- Peripheral ectoWAT → PP hyperinsulinemia & PP hyperglycemia, cardiac diastolic dysfunction
- Lipolytic stage → BCF continues to fall, ghrelin & GH increase, BMI falls, ketogenesis dominates. Microvascular complications & systolic heart failure

Genetic IR predisposes to dysmetabolism. Genetic hepatic IR presents with fasting hyperglycemia → IFG → T2D. Genetic muscle IR presents with PP hyperglycemia → IGT → T2D. Adipose IR, being obesity-resistant, presents as thin phenotype of T2D. This analysis helps to make a rational choice of anti-diabetic therapy.

OGTT & INSULIN RESISTANCE

The hyperinsulinemia observed during 'euglycemic hyperinsulinemia' is a physiological phenomenon and is an adaptive response to increasing amounts of DNL induced endoWAT and does not qualify the use of the term, 'insulin resistance'. However, the ectoWAT accumulation in liver and peripheral tissues does constitute the actual insulin resistance. The endoWAT drives dysmetabolism and dyslipidemia whereas the ectoWAT drives dysglycemia. During and after lipolytic stage, continued calorie surplus causes lipolysis of WAT but not that of the ectoWAT. EctoWAT continues to perpetuate T2D. However, calorie restriction and bariatric surgery depletes hepatic ectoWAT over a period of weeks but requires at least a year to deplete peripheral ectoWAT.



Normal OGTT insulin curve variables and their definations: FPI - fasting plasma insulin (basal); PPI - prandial plasma insulin (120 min); P - peak plasma insulin (60 min); RIR - rate of rise of insulin, formula ((I30-FPI)/30); THETA - angle between insulin secretion arm (0-30 min) & X axis; ZETA - angle between insulin disposal arm (60-120 min) & Y axis; B.C.F. - Beta Cell Function.

Fig. 5a

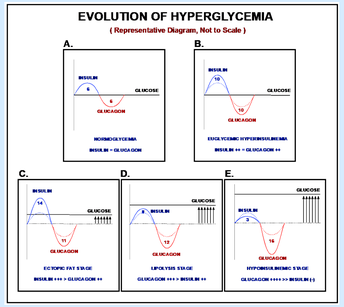


Fig. 5b

CONCLUSIONS

- OGTT with insulin levels is a very useful tool to study the kinetics of glucose and insulin and risk stratify the stage of dysmetabolism.
- The three tier model proposes to explain the physiology of normal metabolism.
- The beta cell and the proposed 'Delta-Gamma system' control the basal metabolism in a flip-flop manner.
- Incretins control the PP metabolism.
- Leptin & ghrelin control appetite and lipid metabolism
- Carbohydrate excess leads to DNL, generating endoWAT which is the root cause of dysmetabolism, dyslipidemia and dysglycemia.
- Ectopic WAT causes 'organ insulin resistance' and leads to dysglycemia.
- Dysmetabolism timeline is proposed which will help to risk stratify and help manage the clinical patient. It will help clinical management of T2D, prediabetes, GDM, PCOS, MAFLD, cardiac failure and obesity. Will be helpful in making a rational choice of anti-diabetic medication.
- Serial assessment will be useful in monitoring intervention and reversal measures.

CONTACT: DR. SURESH N. SHINDE, MD.
91-9822021003
acmepune@yahoo.com

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