Metabolic Syndrome Signaling

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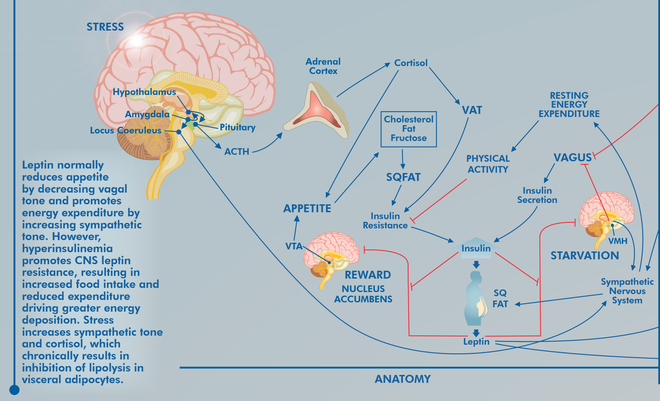
What is Metabolic Syndrome?

A constellation of pathophysiological findings linking ectopic fat deposition, inflammation, insulin resistance, and liver dysfunction with defective glucose and lipid trafficking. Type 2 Diabetes, Non-alcoholic Fatty Liver Disease, Cardiovascular Disease are some of the resultant conditions associated with the syndrome. The three primary drivers of the syndrome are: 1) subcutaneous fat (obesity); 2) visceral fat (stress); and 3) hepatic fat (diet).

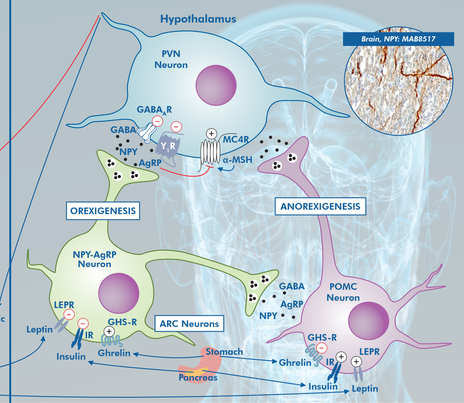
LEGEND

- Phosphorylation
- Activation/Induction/Stimulation
- Inhibition
- Multi-step Process
- Systemic Circulation
- Portal Circulation
- Kinase
- Transcriptional Regulator
- Other

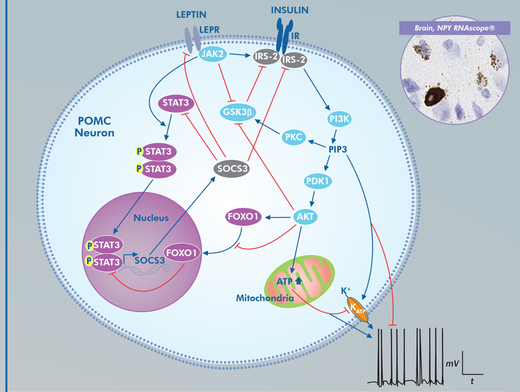
BRAIN



ANATOMY

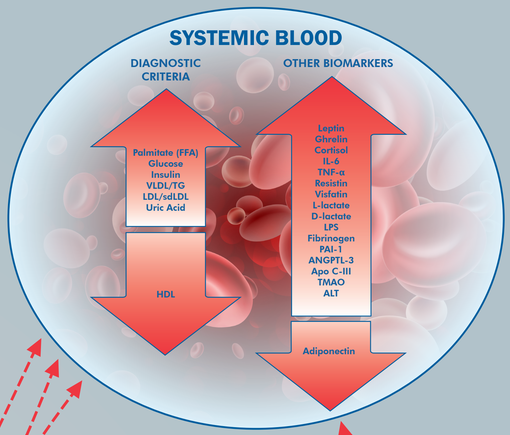


HYPOTHALAMIC CIRCUITRY



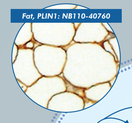
BIOCHEMISTRY/NEUROPHYSIOLOGY

SYSTEMIC BLOOD



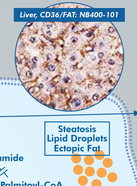
VISCERAL FAT

Visceral adipose tissue (VAT) is acutely responsive to adrenergic innervation which activates hormone-sensitive lipase (HSL) to promote lipolysis. Under chronic stress conditions, cortisol increases NPY production and release from adrenergic synapses. Activation of the Y2 receptors inhibits lipolysis and allows lipogenesis. When the visceral adipocyte becomes insulin resistant, disinhibition of HSL leads to palmitate/FFA efflux into the portal circulation, leading to hepatic uptake, hepatic insulin resistance, and fatty liver. IL-6 efflux into the portal system activates hepatic NADPH oxidase (NOX) resulting in ROS production. Visceral fat contains four-fold more "crown-like structures" that export inflammatory mediators directly to the liver.

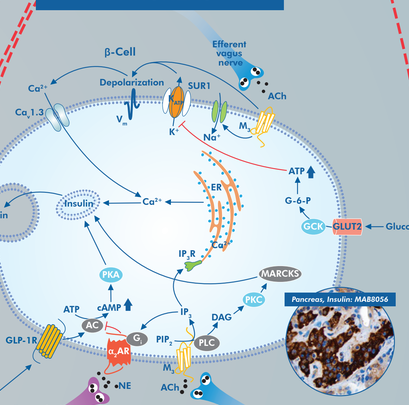


LIVER

Glucose is normally stored as glycogen. However, fructose is shunted to the mitochondria, which become overwhelmed, with resultant shuttling of citrate into the cytosol. This results in de novo lipogenesis, unrelated to insulin levels. Fat will either be exported out as VLDL promoting atherogenesis or result in liver fat droplets which contribute to hepatic insulin resistance. Ceramide and IL-6 inhibit AKT to foment hepatic insulin resistance, resulting in increased hepatic glucose output and hyperglycemia. The effect is compounded by excessive palmitate/free fatty acids (FFA) coming from subcutaneous and visceral fat due to insulin resistance in adipocytes. Peripheral inflammatory mediators (AGEs, LPS, FFA, TNF-alpha) act on JNK-1 to generate reactive oxygen species (ROS), which cause cellular damage.



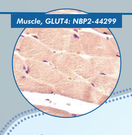
PANCREAS



Insulin release is under tripartite control: a) glucose rise; b) vagus nerve; and c) intestinal GLP-1. Each of these factors is increased in response to poor diet, driving hyperinsulinemia and increased fat storage into subcutaneous and visceral fat.

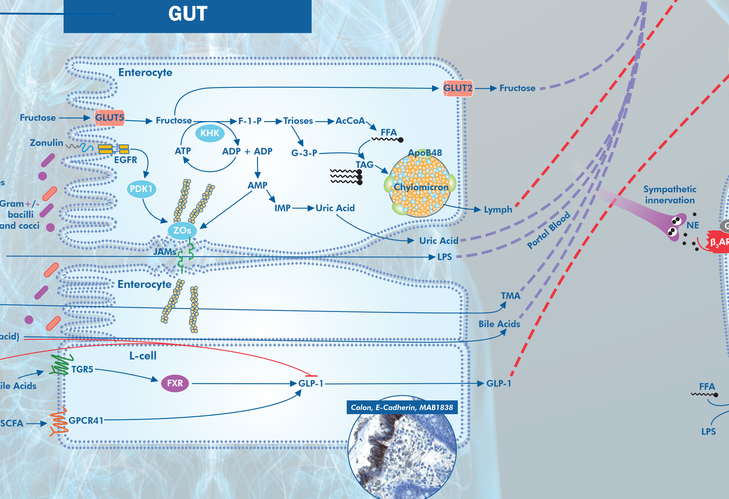
SKELETAL MUSCLE

Increased blood-borne glucose and fatty acids cannot be cleared by skeletal muscle due to insulin resistance and reduction in GLUT4 translocation, which compounds the hyperglycemia.

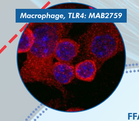


GUT

Intestinal dysbiosis due to poor diet or antibiotics results in lipopolysaccharide (LPS) production. LPS enters the portal circulation due to breakdown in zonulins with resultant "leaky gut", promoting hepatocyte inflammation and hepatic insulin resistance. In addition, lack of dietary fiber results in decreased short-chain fatty acids(SCFA). An increase in bile acid hydrolase leads to a reduction in glucagon-like peptide-1 (GLP-1), inflammation and impaired insulin secretion.



SUBCUTANEOUS FAT



Subcutaneous (SQ) fat is responsive to vagal innervation and hyperinsulinemia, which both activate lipoprotein lipase to drive energy from circulating VLDL and chylomicrons into fat vacuoles to promote fat storage in vesicles. When cells become hypoxic and die, fat tissue is infiltrated with macrophages in "crown-like structures" that promote more insulin resistance through TNF-alpha. Adipocyte insulin resistance disinhibits hormone-sensitive lipase (HSL) leading to palmitate/FFA release into the systemic circulation, which results in hepatic inflammation and insulin resistance. Cell death leads to reduction in adiponectin, which further promotes hepatic insulin resistance.