In The Name Of GOD
لا تعلموا منهم ما لا علمنا عليه من القرآن الكريم حتى تقتلكوا وأيامكم، إنما يتزعمكم الله والعز وسائر الأنبياء الذين أرسله عليهم السلام.
Molecular Aspects of the Energy Balance: Insulin, ROS and Hypothalamic Regulations

By: Javad Saeedi
What is energy balance?

“Energy balance” is the relationship between “energy in” (food calories taken into the body through food and drink) and “energy out” (calories being used in the body for our daily energy requirements).
Types of the energy balance

• When you’re in a **positive energy balance** (more in than out) and when you’re in a **negative energy balance** (more out than in), everything from your metabolism, to your hormonal balance, to your mood is impacted.
Negative energy balance

- A severe negative energy balance can lead to a decline in metabolism, decreases in bone mass, reductions in thyroid hormones, reductions in testosterone levels, and a reduction in physical performance.
Positive energy balance

Overfeeding has its own ramifications not only in terms of weight gain but in terms of health and cellular fitness.
A review on normal physiology of the beta cells and insulin biosynthesis
Cellular aspects of insulin biosynthesis
Molecular aspects of insulin biosynthesis
Low blood glucose

- ATP ↓
- ADP ↑

- Calcium channel closed

High blood glucose

- Calcium channel opened
- Calcium release

- Insulin release
The β-cell K ATP channel is a complex of two different proteins; Kir6.2 and SUR1
Insulin receptor-Insulin binding and signal transduction inside the cell

1. The α-subunit binds insulin (the signal)

2. The β-subunit transmits a signal from bound insulin to the cytoplasm

3. The insulin activates the receptor’s protein kinase domain in the cytoplasm

4. Protein kinases from the receptor phosphorylate insulin-response substrates triggering other chemical responses inside the cell
Activation of Target Cell Receptors by Insulin and the Resulting Cellular Effects

• When insulin is secreted into the blood, it circulates almost entirely in an unbound form; it has a plasma half-life that averages only about 6 minutes, so it is mainly cleared from the circulation within 10 to 15 minutes. Except for that portion of the insulin that combines with receptors in the target cells, the remainder is degraded by the enzyme **insulinase** mainly in the liver, to a lesser extent in the kidneys and muscles, and slightly in most other tissues.
Insulin Promotes Muscle Glucose Uptake and Metabolism

- During much of the day, muscle tissue depends not on glucose for its energy but on fatty acids. The principal reason for this is that the normal resting muscle membrane is only slightly permeable to glucose, except when the muscle fiber is stimulated by insulin; between meals, the amount of insulin that is secreted is too small to promote significant amounts of glucose entry into the muscle cells.
Insulin Promotes Liver Uptake, Storage, and Use of Glucose

- Insulin inactivates liver phosphorylase, the principal enzyme that causes liver glycogen to split into glucose.
- Insulin causes enhanced uptake of glucose from the blood by the liver cells. It does this by increasing the activity of the enzyme glucokinase, which is one of the enzymes that causes the initial phosphorylation of glucose after it diffuses into the liver cells.
- Insulin also increases the activities of the enzymes that promote glycogen synthesis, including especially glycogen synthase, which is responsible for polymerization of the monosaccharide units to form the glycogen molecules.
Insulin Promotes Fat Synthesis and Storage

• Insulin inhibits the action of **hormone-sensitive lipase**. This is the enzyme that causes hydrolysis of the triglycerides already stored in the fat cells.

• *Insulin promotes glucose transport through the cell membrane into the fat cells.*

• Some of this glucose is then used to synthesize minute amounts of fatty acids, but more important, it also forms large quantities of **α-glycerol phosphate**. This substance supplies the *glycerol* that combines with fatty acids to form the triglycerides that are the storage form of fat in adipose cells.
**Insulin**

- ↑ Glucose uptake
- ↑ Lipogenesis
- ↓ Lipolysis

- ↑ Glycogen synthesis
- ↓ Glycogenolysis
- ↓ Gluconeogenesis

- ↑ Glucose uptake
- ↑ Glycogen synthesis
ROS
Mitochondrial ROS Signaling in Organismal Homeostasis

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Generation, transformation, and utilization of organic molecules in support of cellular differentiation, growth, and maintenance are basic tenets that define life. In eukaryotes, mitochondrial oxygen consumption plays a central role in these processes. During the process of oxidative phosphorylation, mitochondria utilize oxygen to generate ATP from organic fuel molecules but in the process also produce reactive oxygen species (ROS). While ROS have long been appreciated for their damage-promoting, detrimental effects, there is now a greater understanding of their roles as signaling molecules. Here, we review mitochondrial ROS-mediated signaling pathways with an emphasis on how they are involved in various basal and adaptive physiological responses that control organismal homeostasis.

Mitochondria and Associated Homeostatic and Stress Signaling Pathways

Mitochondria are essential organelles present in all but a few mammalian cell types, where they perform multiple functions. They are the sites of the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS), through which large amounts of ATP are generated using the electrochemical gradient generated across the inner of two membranes by the electron transport chain (ETC). However, their critical roles in metabolism go far beyond glucose oxidation via OXPHOS and include fatty acid and amino acid metabolism and biosynthesis of hormones, heme, and iron sulfur clusters. Furthermore, in addition to metabolism, mitochondria are involved in apoptosis, ion homeostasis, and innate immunity, with new roles in cell and organismal biology being discovered at an unprecedented rate.

Mitochondria are complex in composition, form, and function. Though often depicted as small round or oval structures, they are instead usually dynamic, branched networks that constantly fuse and divide under control of specific fission and fusion machineries (Mishra and Chan, 2014). Proteomic analyses indicate the overall status of mitochondria is constantly monitored, allowing their number, morphology, distribution, and activity to be modulated by developmental, physiological, and environmental cues. This requires bi-directional signaling pathways that mediate crosstalk between mitochondria and the nucleus. Pioneering studies in budding yeast revealed that mitochondrial dysfunction leads to so-called "retrograde signaling" events that result in adaptive changes in nuclear gene expression and metabolism mediated by specific transcription factors (Butow and Avadhani, 2004). Mitochondrial retrograde signaling pathways also exist in mammals and are now receiving considerable attention because they drive both beneficial and pathogenic adaptive responses.

Given their complicated nature, mitochondrial stress can manifest in many forms that elicit different stress signals. Reduced ETC/OXPHOS capacity can result in cellular energy deprivation (e.g., reduced ATP/energy charge), altered mitochondrial ROS (mtROS) production, or loss of mitochondrial membrane potential, with the precise outcome dictating the specific mitochondrial stress-signaling response (Butow and Avadhani, 2004; Sena and Chandel, 2013). Reduced mitochondrial proteo...
“Reactive oxygen species” (ROS) is usually defined as reactive molecules comprising oxygen ion.
Mitochondrial ROS Signaling Basics

mtROS signaling routes

Thiol PTMs of signaling proteins (e.g. phosphatases)

Activation of redox relay proteins (e.g. peroxiredoxins)

Redox-regulated transcription factors and histone modifiers

Direct nuclear signaling (perinuclear clustering of mitochondria)
Stress oxidative and PBCs

- In the humans, PBCs are one of the most biologically active tissues, and the normal functions of these cells are extremely reliant on oxidative metabolism for ATP synthesis and insulin secretion.
- It has been stated that a disproportion between a high generation of hydrogen peroxidase (H2O2) and low capacity for eliminating the toxicity of it is the crucial reason of aforementioned vulnerability of beta cells.
- The main cause of particularly weak defense mechanism of beta cells against oxidative stress is insufficient action of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX).
Molecular aspects of diabetes mellitus: Resistin, microRNA, and exosome

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Abstract
Diabetes mellitus (DM) is known as one of important common endocrine disorders which could due to deregulation of a variety of cellular and molecular pathways. A large numbers studies indicated that various pathogenesis events including mutation, serin phosphorylation, and increasing/decreasing expression of many genes could contribute to initiation and progression of DM. Insulin resistance is one of important factors which could play critical roles in DM pathogenesis. It has been showed that insulin resistance via targeting a sequence of cellular and molecular pathways (e.g., P3 kinase, PPAR co-activator-1, microRNAs, serine/threonine kinase Akt, and serin phosphorylation) could induce DM. Among of various factors involved in DM pathogenesis, microRNAs, and exosomes have been emerged as effective factors in initiation and progression of DM. A variety of studies indicated that deregulation of these molecules could change behavior of various types of cells and contribute to progression of DM. Resistin is other main factor which is known as signal molecule involved in insulin resistance. Multiple lines evidence indicated that resistin exerts its effects via affecting on glucose metabolism, inhibition of fatty acid uptake and metabolism with affecting on a variety of targets such as CD36, fatty acid transport protein 1, Acetyl-CoA carboxylase, and AMP-activated protein kinase. Here, we summarized various molecular aspects are associated with DM particularly the molecular pathways involved in insulin resistance and resistin in DM. Moreover, we highlighted exosomes and microRNAs as effective players in initiation and progression of DM.

KEYWORDS
diabetes mellitus, exosome, insulin resistance, microRNA, resistin
Insulin Resistance
ROS, Resistin and Energy Balance

- Steppan et al (2001), for the first time used the name resistin (based on insulin resistance) to describe a small protein that was specifically expressed and secreted by mouse adipose tissue and which serum levels increased markedly in experimental models of obesity.
Neural Control of Energy Balance: Translating Circuits to Therapies

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Recent insights into the neural circuits controlling energy balance and glucose homeostasis have rekindled the hope for development of novel treatments for obesity and diabetes. However, many therapies contribute relatively modest beneficial gains with accompanying side effects, and the mechanisms of action for other interventions remain undefined. This Review summarizes current knowledge linking the neural circuits regulating energy and glucose balance with current and potential pharmacotherapeutic and surgical interventions for the treatment of obesity and diabetes.

Introduction
Obesity, diabetes, and associated disorders represent a major public health challenge for North America, Europe, and increasingly the rest of the world. Both obesity and diabetes inflict health and economic burdens that require coordinated strategies to both prevent and treat these disorders. Indeed, a major barrier in the management and prevention of obesity is that weight loss due to lifestyle change alone is inherently difficult. For many, this means that dieting-induced weight loss initially results in tangible beneficial effects but is often followed by a return to previous energy intake and consequently a rebound weight gain.

Numerous neurobiological and physiological mechanisms that regulate energy balance exist. In particular, it has become increasingly evident that the brain plays an important role in sensing energy demands and storage in order to maintain body weight within a rather tight range. Studies ranging from worms, flies, and mice to humans have identified key conserved genes and neural pathways that are critical in regulating energy balance and glucose homeostasis. Moreover, the identification of human mutations in these or analogous pathways has led to hope that it may be possible to develop strategies based on animal model studies that may ultimately lead to successful therapeutic interventions in humans. In this Review, we will highlight how advances in understanding the neurobiological underpinnings of metabolism, including the roles of neurons, hormone and peptide signals, and the interactions between the brain and the endocrine system, have contributed to the development of new therapeutic strategies for the treatment of obesity and diabetes.
Hypothalamus and energy Balance
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<th>Lesions</th>
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<td>Irregular menstrual cycle and loss of libido</td>
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<td>Anterior nucleus</td>
<td>Heat-loss centre</td>
<td>Hyperthermia</td>
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<td>Posterior</td>
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<td>Supraoptic nucleus</td>
<td>ADH secretion</td>
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Schematic Illustration of Hypothalamic Control of Negative Energy Metabolism with Low ROS
Schematic Illustration of Hypothalamic Control of Positive Energy Metabolism with Elevated ROS
Hypothalamus (Arcuate nucleus)

- Hypothalamus
  - Food intake
- Insulin

- Skeletal muscle
- White adipose tissue
- Liver
- Brown adipose tissue
Conclusion

• identification of underlying cellular and molecular procedures that related with energy balance could help to choice better treatment portions for metabolic conditions such as type 2 diabetes mellitus.

• Consumption of sufficient anti-oxidants could protect us against adverse effects of oxidative stress.