Regulation of Brown Versus White Adipogenesis; Mode of Action and Regulatory Mechanism

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Abstract

Mammalian adipose tissue is comprised of two main types of adipocytes, white and brown, which inversely contribute to energy balance regulation. White adipocytes possess a large unilocular lipid droplet, reside in white adipose tissue (WAT), and store excess energy as fat. Brown adipocytes, on the other hand, possess a multilocular appearance (multiple small lipids droplets), reside in brown adipose tissue (BAT), consume energy reserves, and produce heat. Brown adipocytes have an enormous capacity for substrate oxidation conferred by a very high abundance of mitochondria. These mitochondria are equipped with uncoupling protein 1 (UCP1), a 32 kDa protein residing in the inner mitochondrial membrane. When activated by sympathetic nerves that control the lipolytic release of activating fatty acids and the degradation of inhibitory purine nucleotides. White adipocytes possess a large unilocular lipid droplet, reside in white adipose tissue (WAT), and store excess energy as fat. Brown adipocytes, on the other hand, possess a multilocular appearance (multiple small lipids droplets), reside in brown adipose tissue (BAT), consume energy reserves, and produce heat.UCP1 induces a proton leak that uncouples oxygen consumption from ATP production, facilitating macronutrient catabolism. This adaptive mechanism increases energy expenditure and makes BAT an important heater organ, especially in small mammals,there are several factors associated with the formation of brown fat cells such as PGC1α, CIDEA, PRDM16, PPar1α and so on.

Keywords:brown versus white adipogenesis, regulatory mechanism

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Introduction

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abundance of mitochondria. These mitochondria are equipped with uncoupling protein 1 (UCP1), a 32 kDa protein residing in the inner mitochondrial membrane. When activated by sympathetic nerves that control the lipolytic release of activating fatty acids and the degradation of inhibitory purine nucleotides [[1, 2]], UCP1 induces a proton leak that uncouples oxygen consumption from ATP production, facilitating macronutrient catabolism. This adaptive mechanism increases energy expenditure and makes BAT an important heater organ, especially in small mammals [[3, 4]]. The same mechanism is found in brown-like adipocytes which have been given multiple names such as 'inducible', 'beige', or 'brite' (brown-in-white) referring to their brown adipocyte-like appearance and function but are found in WAT depots. Brown and brite adipocytes are distinct cell types, yet their transcriptomic signature and cellular function become remarkably similar under conditions that enforce adaptive heat production [[5-8]]. Brite adipocyte recruitment (a process called 'browning of WAT') is enhanced upon BAT loss, suggesting that these cells complement brown adipocyte functions [[9, 10]].

Nuclear factors regulating brown versus white adipogenesis:

It wasdiscovered that there are several factors associated with the formation of brown fat cells such as PGC1α, CIDEA, PRDM16, PPar1α and so on.

PRDM16:

Is considered the master regulator of brown adipogenesis, as it stimulates differentiation of Myf5-positive myogenic precursor cells into brown fat cells. Increasing the expression of PRDM16 leads to increased expression of BAT selective genes in beige fat cells. PRDM16 is a 140-kDa zinc-finger PR (PRD1–BF1–RIZ1 homologous) which contains protein that stimulates gene expression process as well as oxygen consumption with the brown phenotype. It was shows that PRDM16 has the ability to activate both PGC-1α and PGC-1β so it can induce brown genes while suppressing white genes. Also he suggested that PRDM16 binds to specific transcription factors that related to enhancers of the target gene that this association might determine if PGC-1α, PGC-1β or CtBPs initiates the formation of either a coactivator or corepressor complex. Eventually PRDM16 is needed for mitochondrial biogenesis, oxidative phosphorylation and oxidation of lipids which consider function of BAT **(11)**.

PGC-1α:

It considers one of master regulators of mitochondrial biogenesis and oxidative metabolism in most cell types including brown cells and skeletal muscle. Decrease of genetic expression of PGC-1α leading to reduction in the capacity of cold-induced thermogenesis in vivo in cultured brown fat cells. Expression of PGC-1α induces expression of UCP1 **(12)**.

Studiesshowed that there are groups belonging to steroid receptor coactivator as SRC2/TIF2/GRIP1 played role in suppression of PGC-1α activity and losing of SRC2 function leads to increasing of adaptive thermogenesis and energy expenditure. Lastly, TWIST1 (a helix loop helix containing transcriptional regulator) has been reported as a negative regulator of PGC-1α in brown fat, so suppression of TWIST1 leads to increasing the expression of PGC-1α which

leading to increasing expression of brown fat selective genes. So according to these studies it has been suggested that PGC-1α plays a role in brown fat development and its thermogenic function, but not all of the BAT mass are affected by its reduction **(12)**.

CIDEA:

CIDEA (cell death-inducing DNA fragmentation factor-α-like effector A) was known as their sequence similarity at the N terminal region of the apoptotic DNA fragmentation factor and a member of CIDE family proteins which also include two other types CIDAB and Fsp27 in mice . It has been shown that it has a role in energy hemostasis. In human CIDEA is highly expressed in WAT also inhibiting lipolysis in human adipocyte, but in mice it's highly expressed in the mitochondria of brown adipose tissue. Also is consider a promotor for PPar-α and γ in liver **(13)**.

PPar-α:

Peroxisome proliferator-activator receptors (PPARS) are a group of the superfamily nuclear transcription factors that are responsible for regulation of lipid metabolism. PPar-α was the first genetic sensor for fat discovered in the early 1990's. There were two additional receptors was discovered known as PPar-β and PPar-γ. It played a role in fatty acid oxidation mainly in liver also in skeletal muscle. In PPar-α null mice found that they haven't the ability to meet energy demands during their fasting leading to suffering from hypoglycemia, hyperlipidemia, hypoketonemia and fatty liver. Also it was discovered that PPar-α stimulators increase insulin sensitivity and reduce adiposity and improve hepatic and muscle steatosis. It was discovered that estrogen has effect to PPar-α as it inhibits its activation on obesity and lipid metabolism by targeting PPar-α dependent regulation of target genes **(14)**.

Autocrine and paracrine factors of BAT:

In the past two decades, several molecules where secreted from WAT called adipokines was discovered after the initial discovery of leptin which is a hormone made by adipose cells and enterocytes in the small intestine which regulates energy balance which might induced during brown adipose differentiation or/and thermogenic activation have been identified. Researchers were thought that these adipokines are poorly expressed in BAT which led to assume that BAT only has a limited secretory role, but it has been discovered that BAT has a specific source of regulatory molecules that called adipokines or batokines, these molecules secreted by activated BAT which might expected to support in glucose and lipid metabolism or coordinate with BAT activity with systemic metabolism **(15)**. Although limited direct experimental evidence exists for the specific actions of these batokines, researchers might suggest that some might have autocrine and/or paracrine roles.

Osteopontin (OPN):

Is a glycoprotein which is found in osteoblasts and acts as a bridge between cells and minerals which encoded by the phosphoprotein-1 (SPP1) gene and transcribed into three isoforms OPN-a,-b and -c **(16)**.

OPN was considered as T helper type 1 cytokine which involved in physiological and pathological condition in bone, kidney, inflammation and tumor biology **(16)**. Also, it plays a role in various inflammatory disorders as rheumatoid arthritis atherosclerosis and cardiac fibrosis which all related to obesity also in regulation of immune cell function **(17)**.

OPN is classified into intracellular OPN (iOPN) which is responsible for cell adhesion and movement and secreted OPN (sOPN) which plays a role through its corresponding receptors. It has been shown that OPN mRNA is highly expressed in obese individuals, so it suggested that it plays a role in energy hemostasis, but It has been thought that OPN might have the same capacity as bone morphogenetic proteins (BMPs) which responsible for stimulate browning of WAT as well as OPN might induce the browning of WAT in 3T3-L1 cells via a PI3K-AKT pathway **(19)**.

Sex hormones and energy homeostasis:

Studies reported that sex hormones such as estradiol playing a role in regulation of energy balance. for example, in case of ovariectomized rodents or post-menopausal women resulting estrogen deficiency which leading to increase in body weight, but this can treat by steroid hormones such as inducing phytoestrogen or 17β-estradiol. Any disorder such as obesity, anorexia and cachexia may effect energy metabolism as sex steroids hormones (estrogens, androgens and progestins) are playing an important role in regulation of this metabolism and also may associated with another kind of diseases as diabetes and cardiovascular diabetes **(20)**.

- **Estrogens:** estrogens are steroid hormones which present in high levels in females and low level in males. There are three main forms of estrogens in mammals, estrone (E1), 17β-estradiol (E2) and estriol (E3). E2 is consider the most active metabolite which secreted during premenopausal women in the growing follicles. While during pregnancy, placenta is responsible for producing higher level of estrogens mainly E3 **(21)**.

➢ **Mode of action and regulatory mechanism:**

Estrogens mediate their biological action through binding to estrogen receptor (ER). There are two kinds of these receptors: ERα and ERβ and each one has several isoforms. Activation of ERs occurs through two pathways, classical and nonclassical. The classical pathway involves creating ligand activated transcription factors that form dimers directly binding to an estrogen response element (ERE) producing gene expression. The other nonclassical pathway doesn't include ERE. It might indirectly bind to DNA through protein-protein interactions with other DNA-binding transcription factors **(22)**.

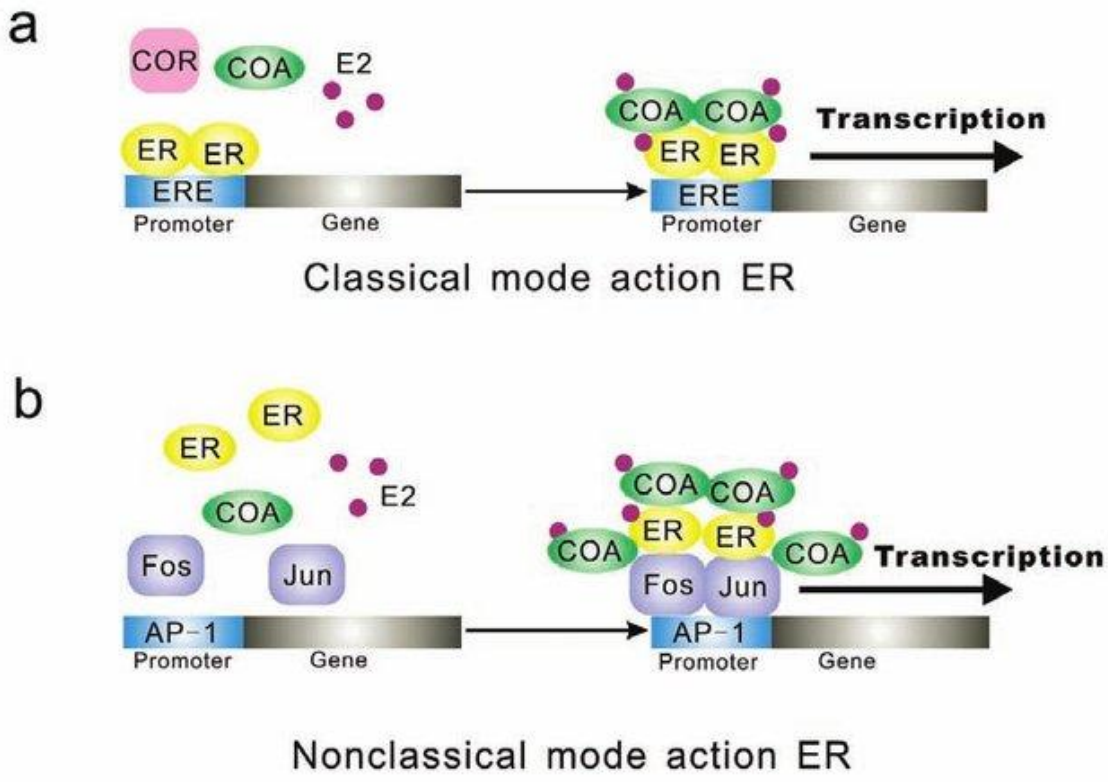

Figure (1): Classical and non-classical mode action ER. (23).

- **Estrogen and control of homeostasis:**

Studies have reported that estradiol played an important role in the control of energy homeostasis centrally through hypothalamus and peripherally through hormonal regulation such as adipokines and insulin. E2 acts at a peripheral level to regulate multiple aspects of energy homeostasis and metabolism. It modulates insulin sensitivity by acting on pancreas, liver, and skeletal muscle. E2 also acts on white adipose tissue (WAT) to control fat distribution, differentiation, and fibrosis and on brown adipose tissue (BAT) to induce thermogenesis. In addition to these effects, E2 also impacts the hypothalamus to regulate BAT function through the sympathetic nervous system (SNS) and food intake. Obesity occurs more often in postmenopausal than premenopausal due to the low level of estrogen. Also, in ovariectomized rats were hyperphagic with higher body weight. Current studies reported that estrogen interferes with fat distribution, differentiation and lipid metabolism. Postmenopausal women suffer from a change in fat distribution which leads to accumulate intra-abdominal fat that was prevented by estrogen supplying. In ovariectomized rats, both central and peripheral administration of estradiol restores fat distribution to normal. Estrogen synthesized in the adipocytes which enhance browning of the adipose tissue; females have a higher metabolic rate than males as well as expression levels of uncoupling protein (UCP-1) **(24)**.

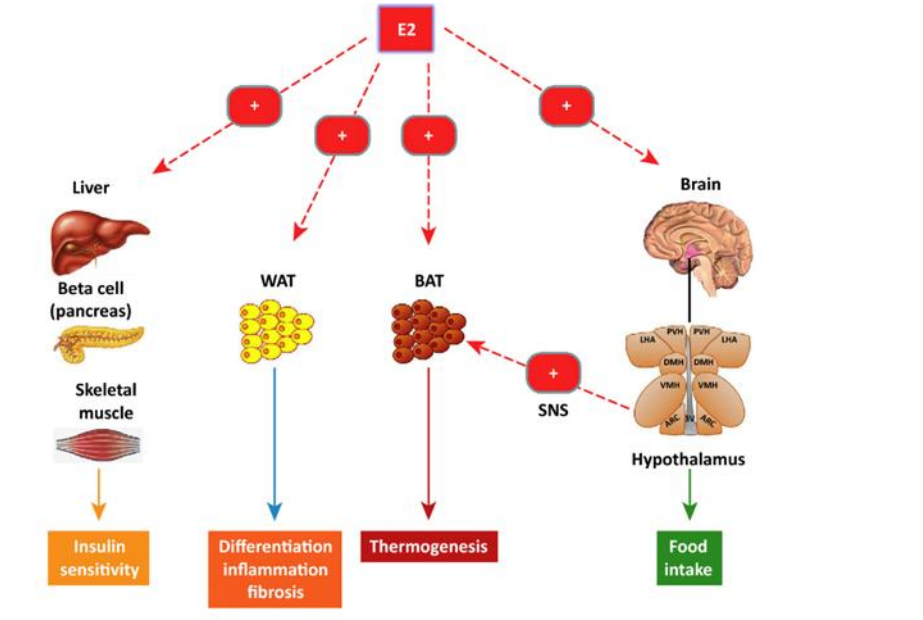

Figure (2): Peripheral and central actions of 17b-estradiol (E2) on the regulation of energy homeostasis. (25).

Phytoestrogens:

Phytoestrogens are nonsteroidal compounds that bind with ERα and Erβ due to their structure which resembles estradiol. the common feature of all phytoestrogens as in shows at least two hydroxyl groups which responsible for the interaction between phytoestrogens and estradiol receptors. that helps in prevention of postmenopausal symptoms and cardiovascular disease (26).

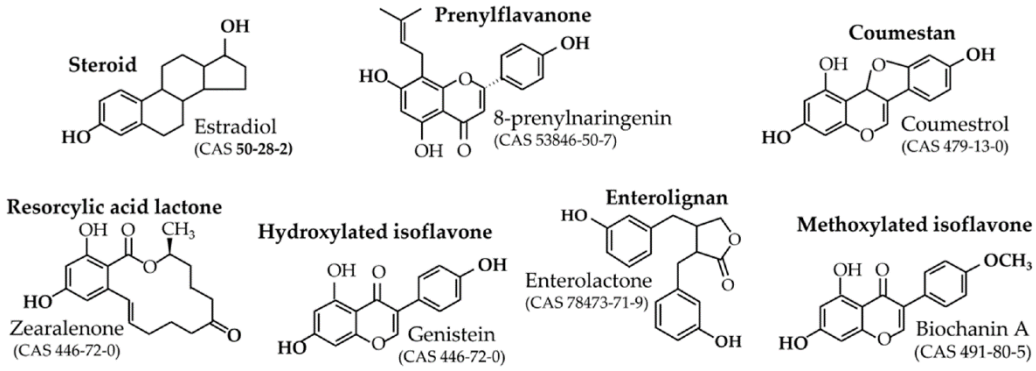

Figure (3): Chemical structures of the main phytoestrogens beside the molecular structure of estradiol (27).

Phytoestrogen divided into two groups: flavonoids (which include isoflavones and coumestans) and non-flavonoids (including lignans and resorcinol derivates). Isoflavones are the largest group in flavonoids that are found in nonactive hydrophilic glycosides such as daizin, genistein and glyctin.in GIT due to presence of β-glucosidases, nonactive isoflavones turned to bioactive isoflavones for example daidzin to daidzein, genistein to genistein and glyctin into glycitein (27).

Isoflavones were found in soybean and soybean derived products (alfalfa, clover, Kudzu root) at different concertation. They consider the most present phytoestrogens in the human environment as soybeans used for both soy-based foodstuffs and transformed foodstuff **(27).** They are a major source of xenoestrogen in both human and animal. Several studies showed that phytoestrogen played a role in reducing obesity and improving glucose control. Also, they showed that exposure mice to phytoestrogens associated with increased energy expenditure, but its metabolic action on lipid metabolism and fat metabolism still not determined **(28).** As it has been shown that phytoestrogen decreases both LDL and total cholesterol levels and increases HDL level. So far, only genistein and resveratrol (RSV) has found that they have direct effect in obesity. In agouti mouse found that genistein supplement protected them from obesity by increasing DNA methylation at the transcription site at agouti mouse **(29).** Also several reviews addressed that there is a link between phytoestrogen and metabolic syndrome which is known to reduce the risk of it. Recent study showed that genistein (GEN) has the ability in browning of WAT and lipid metabolism **(30).**

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