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Editorial

Energy Homeostasis and Peroxisome Proliferator-Activated Receptors

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Energy equilibrium exists when the food intake is equal to energy expenditure of the body. Therefore, a positive energy balance is caused when the food intake is more than the energy expenditure [1]. Hence fundamental to the origin of obesity, BMI equal to or more than 30 kg/m^2 [2], is primarily due to an increased intake of excess calories without appropriate energy expenditure over a long period of time. Endocrinopathies such as Cushing's syndrome, hypothyroidism, etc. were also demonstrated as the primary factors [3,4]. The obesity associated metabolic disorders including cardio vascular diseases and diabetes were alarmingly increased during the last decade.

Communication of peripheral tissues with the central nervous system (CNS) is involved in the energy homeostasis. This complex process is mediated by integrating signals originated from peripheral organs with the central coordination in the brain. The major peripheral organs that participate in the regulation of food intake are stomach, pancreas, gut and adipose tissue [5]. The signals originating from such organs coordinate with that of the CNS and regulate the food ingestion. Appetite and satiety are controlled by a complex system of short-acting and long-acting signals. The appetite is regulated by the hypothalamic arcuate and paraventricular nuclei [6]. Arcuate nucleus of the hypothalamus functions as the main cerebral center in which various signals converge. A balanced interaction between two sets of neurons occurs within the arcuate nucleus to regulate the food intake.

Activation of Neurons secreting neuropeptide Y (NPY) and agouti-related protein (AgRP) neurons promotes food intake (orexigenic effect). NPY/AgRP links to neurons expressing melanin-concentrating hormone and orexins A and B. They promote hunger by acting on brain stem neurons. While activation of cocaine- and amphetamine-regulated transcript (CART) neurons and neurons secreting pro-opiomelanocortin (POMC) stop the food intake (Anorexigenic effect). POMC is cleaved yielding melanocortins, such as α-MSH, that decreases food intake. The activation of NPY/AgRP secreting neurons can also inhibit POMC/CART neurons through the neurotransmitter γ-aminobutyric acid. Furthermore, the endocannabinoid system is also involved in the regulation of food intake, particularly the cannabinoid 1 (CB-1) receptors (encoded by CNR1) and their endogenous ligands, anandamide (N-arachidonoylethanolamine) and 2-arachidonoylglycerol. Hypothalamic levels of endocannabinoids increase during food deprivation [7]. These neurons are integrating their activity with those of peripheral signals.

Stomach and the duodenum secrete the orexigenic peptide ghrelin, which increases before eating and decreases after eating [8]. It can stimulate NPY/AgRP-expressing neurons. Similarly signals from the oral taste receptor are transmitted to the nucleus tractus solitarius (NTS) in the hindbrain by afferent sensory fibres. Satiety signals are transmitted to the brain via vagal afferent fibres from the gut that synapses in the NTS, which participates in gustatory, satiety, and visceral sensation.

An anorexigenic effect of insulin has mediated through the arcuate nucleus. After the food ingestion, Peptide YY is secreted by the gastrointestinal tract might have an anorexigenic effect [9]. While the glucagon-like peptide 1 is secreted from the proximal gastrointestinal tract in response to food ingestion exerts slight anorexic effects. Satiety is also mediated by other gut proteins, such as cholecystokinin (CCK). Among the peripheral organs adipose tissue is very important in maintaining the energy homeostasis.

The afferent signals from adipose tissue and the efferent signals from CNS to the peripheral organs operate in a coordinated manner to maintain the energy homeostasis. The adipokines regulate the utilization of substrates for energy between adipose as well as non-adipose tissues [10]. Among the adipokines, leptin and adiponectin are central to the energy homeostasis. Leptin (16 kDa) serves as a major anorexigenic signal. It exerts long-term control by activating catabolic circuits and by inhibiting anabolic circuits. α-MSH is found to be an intermediate in leptin signalling [11]. Leptin stimulates the pathways that favor fatty acid oxidation and decreases lipogenesis. Furthermore, it can also decrease the ectopic deposition of fat in liver or muscle. Leptin directly increases hepatic lipid oxidation and lipolysis in skeletal muscle. Similarly, adiponectin- a 244 amino acid with 30 kDa protein- stimulates in-

creased insulin sensitivity and decreases hepatic glucose production by augmenting glucose utilization in muscle.It can also increase fatty acid oxidation in muscle and liver. Adiponectin receptors can activate the peroxisome proliferators activated receptors (PPARα), which in turn regulates fatty acid metabolism [12].

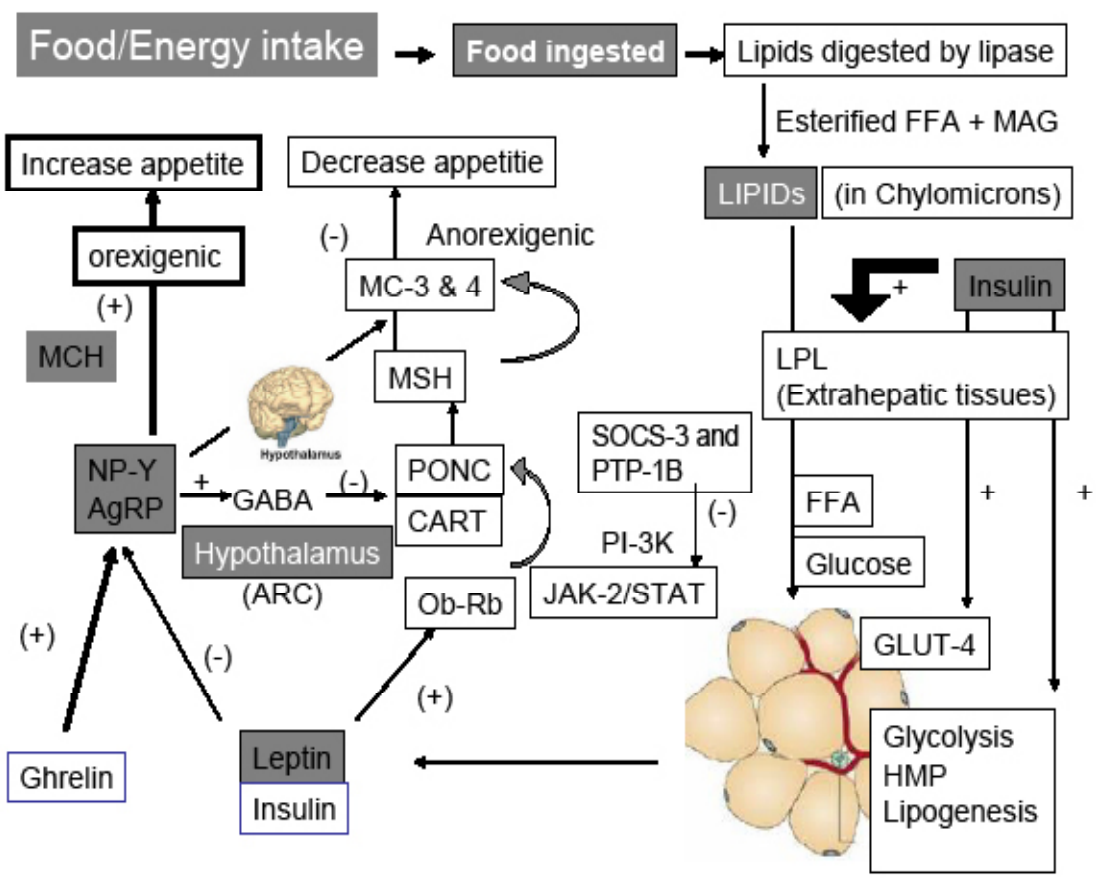

Figure: Integrating signals from peripheral organs with central coordination in the brain. Ob-Rb: Receptor for Leptin in CNS; MC-3 and 4: Receptor for Melanocyte Stimulating Hormones MSH; LPL: Lipoprotein Lipase; GLUT-4: Glucose Transporter-4; STAT: Signal Transducer and Activator of Transcription; POMC: Proopiomelanocortin; JAK2: Janus Activating Kinase; PI-3K: Phosphoinositide-3 Kinase; CART: Cocaine-and Amphetamine Regulated Transcript; SOCS3: Suppressor of Cytokine Signaling 3; PTP1B: Protein Tyrosine Phosphatase, Non-Receptor.

The process of lipogenesis and lipolysis at adipose tissue is mediated through members of the steroid/retinoid nuclear receptors super family transcription factor, peroxisome proliferator-activated receptor (PPAR). Among the three types of PPARs identified i.e. alpha (α), gamma (γ), and delta/beta [13], two isoforms PPAR gamma such as Gamma1 and 2 are expressed in non-adipose and adipose tissues, respectively. In general, fatty acids or their derivatives activate PPAR-γ. It enhances insulin sensitivity, adipogenesis and has role in placental function. Equilibrium between PPAR-α and PPAR-γ activities is required for the maintenance of lipid oxidation and synthesis respectively. In liver and skeletal muscle, PPAR-α regulates the expression of genes involved in peroxisomal and mitochondrial beta-oxidation. PPAR-γ2 favours the deposition of excess calories as triacyl glycerol (TAG) in adipocytes. PPAR-γ2 is found to be involved in growth arrest, clonal expansion and early and terminal differentiation of adipocytes [14]. It also modulates adipocytes differentiation and production of cytokines.

Anti-hyperglycemic adipokines are secreted by activation of PPAR-γ. This shifts the non-essential fatty acids deposition as TAG in adipose tissue. Thus, there will be a net shifting of fat from liver to adipose tissue. Moreover, adiponectin can increase the PPAR-γ in adipose tissue. This process will enhance the anti-inflammatory effect and thus the insulin sensitivity in the adipose tissue. Proteins for the transport of fatty acids across the plasma membrane, cytosol and oxidation were increased by PPAR-activation. In clinical practice PPAR-α agonists, fibrates are available to improve dyslipidemia. PPAR-γ agonists, thiazolidinedione (TZD) class of drugs such as rosiglitazone and pioglitazone provides similar effects on glycemic control.

Patients with 27 to 29.9 kg/m^2 BMI plus co-morbidities or those with BMI of ≥ 30 kg/m^2 even in the absence of co-morbidities, were recommended for pharmacotherapy. But adverse effects of TZD drugs such as weight gain, myopathy and rhabdomyolysis, increase in plasma creatinine and homocysteine, fluid retention, peripheral edema, and potential risk of cardiac failure limited the use of these classes of drugs.

Nevertheless, PPAR-γ remains the major target for new non-TZD class of drugs development useful in the treatment of obesity and associated metabolic disorders. Soy protein activates PPAR-γ in adipose tissue, preventing adipocyte hypertrophy and metabolic abnormalities during obesity. Novel TZD analogs, Efatutazone (third generation) and Balaglitazone (second generation partial agonist developed by Dr. Reddy's laboratories, India) are effective PPAR-γ agonist, currently being evaluated in phase III clinical trials [15]. Agonist such as SPPAR gammaM5 ((2S)-2-(2-chloro-5-{[3-(4-chlorophenoxy)-2-methyl-6-(trifluoromethoxy)-1H-indol-1-l] methyl} phenoxy) propionic acid), has also been developed with notable insulin sensitizing properties and superior tolerability profile to that of rosiglitazone [16]. PAR-1622, a partial activator, against PPAR-γ has excellent antihyperglycemic activity and a broad safety profile [17].Synthetic PPAR-γ ligands, INT-131, and T2384 are also being evaluated in the phase trials [18,19].

Medications for weight loss in combination with lifestyle modifications rather than single therapy recommended as well [20]. Being the central role of PPAR-α and PPAR-γ in the regulation of energy balance, more effective agonist is required to treat the obesity-associated morbidities.

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