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PATHOPHYSIOLOGY OF OBESITY- AN INSIGHT INTO THE MOLECULAR MECHANISM

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ABSTRACT

Obesity is a multi factorial disease which involves complex molecular pathways is basically due to imbalance between energy intake and energy expenditure.Presumably other than genetic endowments, a series of biological events tip the fine balance of homeostatic mechanism of energy control and any shift in these regulatory pathways can result in obesity. Though the effect is not always predictable, once the homeostasis is altered it is very difficult to restore the balance. The primary regulating centre of energy intake is brain; the hypothalamus being the main integrating centre. The regulation of energy expenditure is still not clear. With very few pharmaceutical agents to curb this emerging public health problem, a better understanding of molecular mechanism of energy imbalance is well appreciated. This article gives an overview of molecular mechanism of patho physiology of obesity.

KEYWORDS: **Obesity, Energy balance, Homeostasis, Molecular mechanism, Pathophysiology**

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INTRODUCTION

Obesity is a disease that develops from complex interactions of multi factorial origin. Now it has become apparent that susceptibility to obesity is largely dependent on interaction of many genes and gene polymorphisms.[1] Presumably other than genetic endowments, a series of biological events tip the fine balance of homeostatic mechanism of energy control and any shift in these regulatory pathways can result in obesity.[2] Though the effect is not always predictable, once the homeostasis is altered it is very difficult to restore the balance.[3]The management of obesity is still a topic of uncertainty. Promotion of healthy eating patterns, maintenance of healthier body weight, psychosocial well being and increase physical activities are primary steps followed by therapeutic management and surgery. Once disease is established it is irreversible by the available measures and only few drugs are there in the market. Surgery though an effective measure; the patient compliance seems to be less.[3, 4] Other than achieving primary goal of treating this disorder, therapy should also be able to prevent its complications; cardiovascular disease, hypertension, dyslipidaemia, endothelial dysfunction, polycystic ovarian disorder, type-2 diabetes mellitus, impaired glucose tolerance being some of them.[4]With very few pharmaceutical agents to curb this emerging public health problem, a better understanding of molecular mechanism of this energy imbalance is well appreciated.

HOMEOSTATIC CONTROL OF ENERGY BALANCE

Energy balance equation states that energy intake is equal to sum of energy expenditure and energy storage.[5] (fig1)Obesity is a disorder of shift in the controlling pathways of the energy homeostasis.[6] Diverse neural endocrine and metabolic signals orchestrate these pathways which control energy intake and energy expenditure.[7] These regulating pathways can be central and peripheral.

REGULATION OF ENERGY INTAKE

The primary centre is in the brain .The arcuate nucleus (infundibular nucleus) in the mediobasal hypothalamus and perifornical region in the lateral hypothalamus are the key sites. It forms the main integrating centre for various metabolic inputs about the peripheral energy state. It has complex interactions with other parts of hypothalamus like paraventricular nucleus and the ventro medial hypothalamus. Other sites in the brain such as the nucleus accumbens, the amygdala and nucleus tractus solitarius in the medulla are also important.

AFFERENT COMPONENTS IN ENERGY HOMEOSTASIS

The hypothalamic neuronal circuits in arcuate nucleus consist of two groups of opposing neurons. In one group Peptide Neuropeptide Y (NPY), Agouti related protein (AgRP) controlling anabolic pathway stimulating food intake, reducing energy expenditure and promote weight gain. They are orexigenic or appetite stimulating[8] (fig 2) and contribute to weight gain and obesity.In the other group Prepro Opio Melanocortin (POMC) and Cocaine, Amphetamine related transcript (CART) which secrete alpha melanocyte stimulating hormone (alpha -MSH) controlling catabolic pathway reducing food intake and subsequently activating $5HT_{2c}$ (serotonin) receptors. They are anorexigenic or appetite suppressing.[9] (fig2).Their activity seems to be reduced in obesity. The network also includes Serotoninergic,Catecholaminergic, Endocannabinoid and Opioid signalling pathways. Monoamines such as NorAdrenaline, dopamine and 5 –hydroxy tryptamine (5HT) can modulate satiety signals. Of these nor adrenaline exist with NPY neurons and is appetite promoting and contributing to obesity. Agonist action of 5HTc receptor and deficiency of dopamine are anorexigenic.Two major groups of inputs inform the brain short-term signals produced by the gut system (satiety signals) and long-term signals produced by

adipose tissue (Adiposity signals). Among inputs from other parts of CNS, that from the nucleus accumbens regulates hedonic aspects of feeding behaviour i.e. aspects of eating driven by pleasure or reward. This hypothalamic centre contains large amounts of cannabinoid receptors (CB1) and administration of cannabinoids both endogenous and exogenous provokes a powerful feeding behaviour. Stress and other environmental factors can modulate this system. Food intake initiates a series of signals; of these satiety signals through the brain stem while adiposity signals via the blood-brain barrier reach the hypothalamus, the integrating centre. Various peripheral organs with its neurohormonal, sensory and other cytokine signalling pathways also send inputs to this homeostatic system.[10] Any imbalance in this system can upset energy homeostasis.

Adiposity signals

Adipose tissue through its peptides leptin, adiponectin, and resistin send *Adiposity signals* about the fat store to the hypothalamus. Of these hormone leptin discovered in 1994 plays a prominent role in mediating long-term appetite controls ie to eat more when fat storages are low and less when fat storages are high.[11] It is the primary messenger sending two signals, one to the brain satiety centre and other to the fat inside cells to break down it into a kind of fat that can be burned as energy.[12] There are receptors for leptin in arcuate nucleus. When leptin level falls orexigenic neurons are activated and food intake is increased .There is an anabolic effect manifested by increased synthesis and storage of fat and decreased energy expenditure .When leptin level rises the anorexigenic neurons are activated and catabolic effect.[13] The protein adiponectin levels are seemed to be reduced in obesity and it enhances insulin sensitivity; has vascular protective effects. Resistin and RBP4 levels are increased in obesity and may induce insulin resistance.[14] In addition to this adipose tissue release certain factors which can affect peripheral tissues which includes cytokines like Tumor Necrosis Factor (TNF) -α,Inter leukin (IL)-6, complement factors such as factor D or adipsin, enzymes aromatase 11 beta-HSD -1, substrates like free fatty acids, glycerol, prothrombotic agents such as plasminogen activator Inhibitor -1 and blood pressure regulating angiotensinogen.[15] Adipose tissue which is differentiated from mesenchymal periadipocytes by a series of steps mediated by specific transcription factors; is now considered as a true endocrine gland, secreting peptide hormones together called adipokines which play a prominent role in the patho physiology of obesity[16]

Satiety signals

The adiposity signals are integrated with neurosensory satiety signals from stomach, liver and GIT.[17]Various peptide hormones are released from the gut during feeding.[18] These blood-borne hormones are the most important which bring information from viscera and are sensed by receptors on vagal and other afferents. They relay in nucleus tractus solitarius and modify the neuronal circuit.[19] They can control food intake, meal size and feeling of satiety or hunger.[20] Ghrelin is a hormone produced by the stomach modulating short-term appetitive control- to eat when the stomach is empty and to stop when the stomach is stretched. Various endocrine signals with complex signalling pathways are produced by hormones including GLP-1, Oxycyntomodulin, Peptide YY, Cholecystokinin, Pancreatic polypeptide, Amylin which are secreted from small intestine. Ghrelin, convey sensation of hunger, CCK conveying satiety signals, PYY_{3-36} conveying satiation to the hind brain by direct action or through vagus.[21] (fig 3)In addition to this, bombesin family of molecules like bombesin, neuromedin B, neuromedin C, gastrin releasing peptides can suppress food intake while incretin family of peptides like glucagon-like peptide -1, increase insulin release, inhibit glucagon release, delay gastric emptying and thereby lowers blood glucose.[22] The metabolites like glucose; ketones can also influence expression and release of various hypothalamic peptides in this appetite control network. It has been observed that altered patterns of secretion of several gut

hormones, which occur after surgical procedures results in substantial, permanent weight loss, despite significant peri operative risks.[23] These observations have encouraged research into the role of gut hormones in regulating appetite and body weight, and potential new targets in the development of anti-obesity medications.[24]

INTEGRATION OF SIGNALS

There is a central autonomic pathway connecting the relay stations of adiposity and satiety signals. In addition there are controlling pathways connecting signals from adipose tissue and GIT; that reach the hypothalamus. These signals get integrated in the arcuate nucleus of hypothalamus with other sensory, cognitive and environmental signals from the cerebral cortex.[17]The brain processes these integrated signals and generate neuronal and hormonal outputs to balance energy intake with expenditure.[25] After central integration of the inputs, the brain produce its output mainly to the Feeding centre (Lateral Hypothamus)) and Satiety centre (Ventromedial hypothalamus).Final effects in energy homeostasis are realised by the brain stem motor system which control feeding behaviour. It is manifested as neuroendocrine activation from the hypothalamo pituitary gland; autonomic activities by stimulation of sympathetic nervous system and motor behaviours like eating.[26]

REGULATION OF ENERGY EXPENDITURE

The sympathetic nervous system through its beta 3 adrenergic receptor stimulates lipolysis in White Adipose Tissue (WAT) and thermogenesis in brown adipose tissue (BAT) via uncoupling proteins.[27]

The components of the system that regulate energy expenditure are resting or basal metabolic rate, Non Exercise Activity thermo genesis (NEAT), physical activities, cardio respiratory work, actions of various metabolic enzymes and sympathetic nervous system.[28]

The resting metabolic rate which accounts for 60-70%of daily energy expenditure is the energy utilized during rest for normal physiological processes and maintenance of normal body temperature.[29] Non Exercise Activity Thermogenic processes include energy expended for food consumption, which constitutes approximately 10% of daily energy expenditure, maintaining posture ,spontaneous muscle contraction, energy spend during hormonal variations and psychological stresses.[29] Physical activities and other components accounts for 20-30% of energy expenditure.[30] The molecular mechanism of this regulation is still not clear.

EFFERENT COMPONENTS IN ENERGY HOMEOSTASIS

Both brown and white adipose tissues have a major role in thermo genesis. The colour of brown adipose tissue (BAT) attributed to high density mitochondria and white adipose tissue (WAT) to fat cells[31]. BAT is richly innervated by the sympathetic nervous system. Animal experiments have proved that mitochondrial uncoupling protein (UCP) and its various isoforms UCP-1, UCP-2, UCP3 are found in brown fat. These proteins uncouple oxidative phosphorylation so that mitochondria continue oxidative metabolism but produce much less ATP and more heat.[32]

Beta 3 adreno receptor agonists in obesity

Functional B3 adreno receptors are present human white adipocytes and brown adipocytes. Other tissues in human expressing beta3 adreno receptors are heart, brain, colon, urinary bladder, skeletal muscle, ureters, stomach, myometrium , small intestine, gall bladder, and prostate. The beta3 differ from beta 1 and beta2 structurally and pharmacologically. There are three different forms of beta3; form A , form B and form C which differ in the number of amino acids. Form A, has 396 amino acids, form B, 12 amino acids and form C, 6 amino acids.[33]

Structure and regulation of beta 3 receptors.

They are G proteins with alpha, beta, gamma subunits. They are serpentine transmembrane proteins with extracellular amino terminal (N terminal) and intracellular C terminal. The extracellular domain traverses the membrane seven times forming three extracellular loops

and three intracellular loops.[34] Unlike Beta 1 and Beta2 the C terminal of Beta3 do not possess phosphorylation site for protein kinase A or beta receptor kinase (beta ARK). [33] The transmembrane domains two and seven are responsible for G protein activation and initiation of pharmacological effect. Transmembrane domains three, four, five and six are essential for the interaction with the ligand.[33] The alpha subunits carry GDP molecules .G proteins are coupled to effectors proteins and these second messengers regulate the activity of these receptors.[34] The beta 3 receptors coupled to Gs proteins increase adenyl cyclise activity and increases cyclic AMP level. Those coupled to Gi proteins decreases intracellular cyclic AMP. CAMP dependant stimulation of UCP1 in brown adipocytes by beta 3 adreno receptors needs MAP kinase p38. MAP kinase p38 (mitogen-activated protein kinase p38) activation occur via protein kinase A. Role of beta 3 in thermogenesis and lipolysis especially by sympathetic stimulation in rodents have been proved.[33] Interestingly, in spite of experiments and long term trials on beta 3 receptors, a clinically effective beta 3 agonist against obesity is nowhere in drug armamentarium.[33] The main possible reasons are poor expression of beta 3 receptors in human white adipocytes, less quantity of brown adipocytes, wide variations in pharmacology of human and rodent adipocytes.. In addition to mutation of B3 receptor; alteration of leptin gene, leptin receptor gene, leptin deficiency, Pro Opio Melano Cortin (POMC) gene, brown adipose tissue gene, over expression of GLUT-4 can cause imbalance of energy homeostasis.[35]

CONCLUSION

A gamut of factors regulates energy homeostasis and the pathophysiology of obesity is mainly attributed to alteration in the molecular mechanism of these controlling pathways. The defects can be in the pathways controlling energy intake manifested as deficiency in the synthesis or action of leptin and other gut hormones, defects in the hypothalamo neuronal system responding to these signals or it can be defects in the system controlling energy expenditure. Even though exact regulation of energy expenditure is unknown reduction in the function of beta3 adreno receptor gene; resulting in decreased thermogenesis in brown fat and altered lipolysis in white fat or dysfunction of the proteins that uncouple oxidative phosphorylation have a role. All these point out the importance of pharmacogenomis and need for more genetic based studies for controlling this global phenomenon.

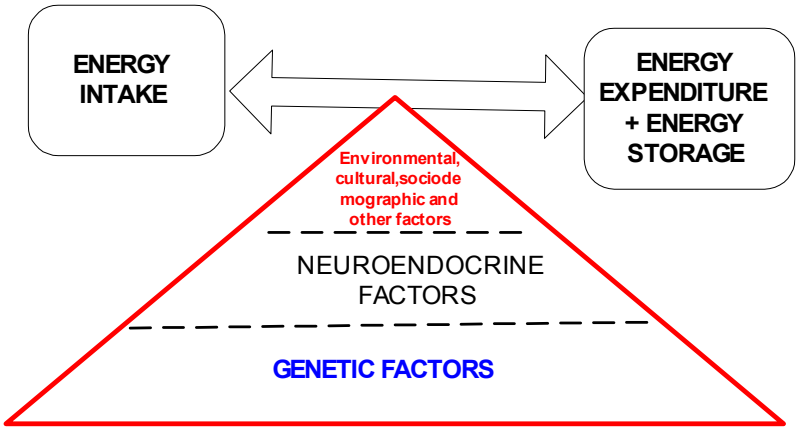

Figure 1
Energy balance

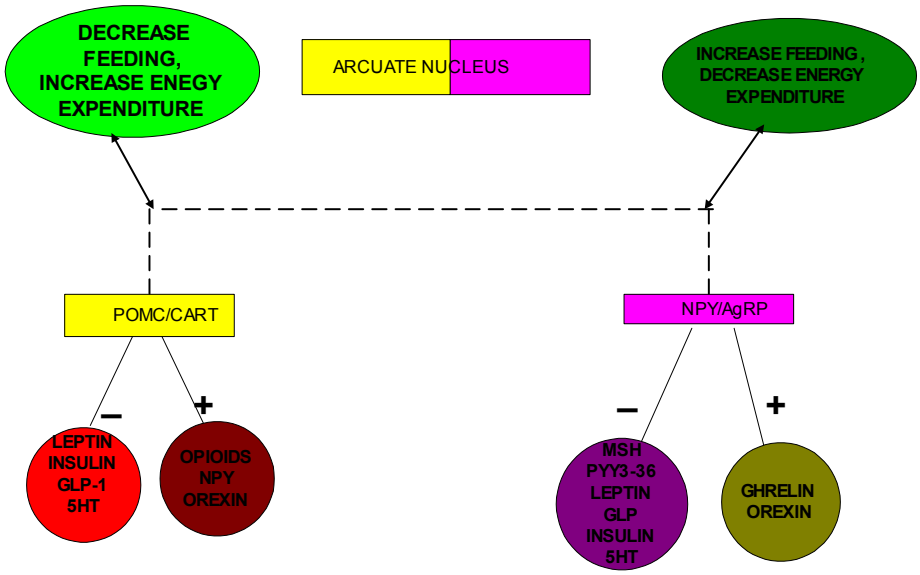

Figure 2
Hypothalamic regulation

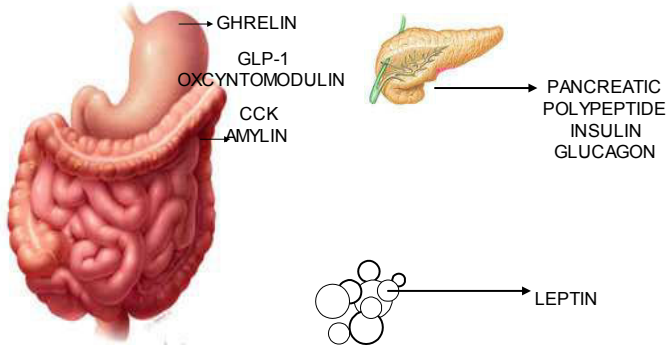

Figure 3
Peripheral hormones

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