

## AETIOPATHOGENESIS OF OBESITY

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**Abstract :** Obesity is a problem of energy balance, which develops when energy intake is more than the total energy expenditure (BMR, Thermogenic Physical Activity & Non Exercise Activity Thermo genesis). Adipose tissue consists of adipocytes which store the lipids, and also produce various molecules which affect the body's energy management like leptin, adiponectin, adipisin, resistin etc. Leptin has been proven to be the principal afferent signal in the negative feedback loop regulating the size of the adipose tissue mass, thereby regulating obesity. Leptin receptors are found in hypothalamus, where an increase in leptin level, leads to decreased appetite and increased energy expenditure, via Melanocyte Stimulating Hormone (MSH). Low leptin levels stimulate Neuropeptide Y, causing an increase in food intake and decreased energy expenditure. Obesity results from either impaired secretion of leptin, or due to resistance to the action of leptin. Ghrelin, which is an endogenous ligand for the growth hormone secretagogue receptor, when secreted into the plasma by neuroendocrine cells of stomach, acts on hypothalamus via Neuropeptide Y & Agouti Related Peptide (AgRP), which are potent orexigenic peptides. Stomach has an important role in energy homeostasis, apart from ghrelin release, gastric distension and emptying play an important role in regulating food intake. Various molecules like cholecystokinin and enterostatin act on stomach and inhibit gastric emptying, thereby reducing food intake. Hypothalamus is the central agency for integration of all signals for maintenance of energy balance of body. Orexin, Melanin Concentrating Hormone, NP-Y and AgRP stimulate appetite, while MSH and GLP-1 suppress appetite. Knowledge of molecular basis of the signalling will help modulate therapeutic measures for obesity.

### INTRODUCTION

Obesity has gone from being a merely medical diagnosis to a morbid state with widespread physical, mental and social ramifications. No disorder can be effectively managed if its cause is not known and blaming obesity on the gluttonous habits of the person is not tenable any longer<sup>1</sup>. We are still unravelling the interlinking and intertwined threads of metabolism that make up the complex tapestry of obesity. This review is an overview of the latest research available in medical literature on the aetiopathogenesis of obesity.

### ADIPOSE TISSUE

At the basic level obesity occurs whenever the energy expenditure falls behind the energy intake leading to the body storing the excess energy as adipose tissue. As with all human physiology there is a homeostatic loop involving energy intake and disposal; with the adipose tissue itself playing a vital part. Adipose tissue consists of the much maligned adipocyte which stores the lipids in its cytoplasm and the stromal and vascular framework from which the preadipocytes are derived. However the adipocyte is not content just to act as a lipid store but also moonlights as a prolific endocrine cell producing various molecules which affect the body's energy management<sup>2</sup>. Leptin is the major molecule secreted that has been extensively studied and is discussed in detail below. Other molecules include Adiponectin which enhances insulin sensitivity and lipid oxidation; adipisin or Factor D a complement molecule; resistin which contributes to insulin resistance. A less understood part is the role of Brown Adipose Tissue (BAT). In

essence BAT contains an enzyme which decouples the oxidative respiratory chain from ATP generation leading to dissipation of the energy as heat. In mice BAT activity is increased by the sympathetic stimulation mediated by leptin leading to thermogenic dissipation of energy<sup>3</sup>. Mice deficient in BAT become obese and might become diabetic. Stimulation of the BAT by  $\beta$ 3 agonists on the other hand would protect the mice from obesity<sup>4</sup>

### LEPTIN

Leptin (leptos – greek: thin) circulates as a protein of relative molecular mass 16,000 in mouse and human plasma<sup>5</sup>. It was initially conceptualised during experiments on mice in which recessive mutations in the obese (ob) and diabetes (db) genes lead to obesity and diabetes resembling human morbid obesity<sup>6</sup>. It was postulated on the basis of further cross circulation experiments that the ob gene encoded for a circulating factor that regulated energy balance and that the db gene encoded the receptor for this factor<sup>6</sup>. This was confirmed when leptin RNA was found to be expressed in adipocytes and the plasma levels of leptin were highly correlated with adipose tissue mass<sup>7</sup>. Leptin levels underwent a sharp fall in both humans and mice after weight loss<sup>7</sup>. Obese humans tend to have high levels of leptin thus making leptin the principal afferent signal in the negative feedback loop regulating the size of the adipose tissue mass. As would be expected administration of leptin by injection results in a dose dependent decrease in body weight and this weight loss is restricted to the adipose tissue mass with sparing of lean body mass<sup>8</sup>. The leptin receptor (Ob – R) is encoded by the db gene. It is a member of the cytokine family of receptors first isolated in the choroid plexus of mice<sup>9</sup>. Mutations in the Ob – R result in an obese phenotype identical to ob mice indicating Ob – R essentiality in leptin action. The leptin

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receptor is expressed in high levels in the hypothalamic neurons. Low leptin levels lead to stimulation of neuropeptide Y or its receptors; Neuropeptide Y being the most potent orexigenic stimulus when administered intrathecally<sup>10</sup>. This then leads to the starvation response including an increased food intake, decreased energy expenditure,  $\bar{GHRH}$  and  $\bar{GnRH}$ . Weight gain and a consequent increased leptin acts through the Melanocyte Stimulating Hormone (MSH) and its precursor Proopiomelanocortin (POMC) in the hypothalamus resulting in a decreased food intake and increased energy expenditure<sup>11</sup>. Leptin appears to act within a largely long term system of controlling feeding behaviour and energy balance and influences the quantity of food consumed relative to the amount of energy expended.

This nearly perfect Leptin system of long term energy balance can go wrong at three sites<sup>12</sup>

1. Failure to produce leptin: as occurs in ob/ob mice; analogous to type 1 diabetes mellitus. Several families with early onset morbid obesity caused by inactivating mutations in leptin have been described<sup>13</sup>.
2. Inappropriately low leptin secretion for a given fat mass. In such patients the adipose tissue would expand until normal leptin levels are reached thus resulting in obesity.
3. Relative or absolute insensitivity to leptin at its site of action: as occurs in db/db mice; analogous to type 2 diabetes mellitus. Such patients will usually have high circulating leptin levels. The resistance might be at the receptor level in form of mutations of the db gene. Mechanisms of resistance could also involve POMC mutations preventing synthesis of MSH & mutations involving the melanocortin 4 receptor<sup>14</sup>. Involvement of peptide processing enzymes Carboxypeptidase E (product of the *fat* gene) and PC-1 leads to obesity and hyperleptinaemia in mice; as does mutation of the *tub* gene. Additionally the entry of leptin into the cerebrospinal fluid may be limiting in some patients and morbid obesity could result when the plasma leptin levels exceed the capacity of the transport system<sup>15</sup>.

The above mentioned mutations are a rare cause of human obesity. The exact aetiology of common obesity is still unknown there being no evidence of polymorphisms of leptin or leptin receptor gene among the common forms of obesity<sup>16</sup>.

## GHRELIN

Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor (GHS receptor)<sup>17</sup>. GHSs were a non natural synthetic group of molecules developed as a research tool<sup>18</sup>. GHSs act on a G protein coupled receptor (GHS Receptor type Ia – GHS-RIa) distinct from that of GHRH. Tomassetto et al isolated ghrelin as the 'motilin related peptide' with structural and effect related similarities to the duodenal hormone motilin and Kojima et al correctly identified it as the endogenous ligand for the GHS-RIa receptor which is predominantly expressed in the pituitary and the hypothalamus<sup>17,19</sup>.

Ghrelin itself is expressed mainly in the stomach by neuroendocrine cells (P/D1 cells in humans) in the fundus and is secreted into the circulation. Ghrelin concentrations in the plasma rise progressively during fasting and fall to a nadir within an hour of refeeding. Both open and closed gastric ghrelin cells exist in the stomach suggesting

they receive both luminal and neuroendocrine information. Gastric ghrelin production is regulated by nutritional and hormonal factors. Inhibitory signals include somatostatin, interleukin 1 $\beta$ , growth hormone, high fat diet and vagal tone. Fasting and low protein diet leads to increased expression and plasma concentrations of ghrelin. This is in contrast to majority of gut hormones whose secretion increases with food intake and decreases with fasting. Ghrelin administered into the periphery or cerebral ventricles potently stimulates food intake leading to weight gain in rodents<sup>20</sup>. The premeal increase of ghrelin may trigger the desire to eat in animals and humans. Ghrelin secreted into the plasma acts on the hypothalamus through Neuropeptide Y (NPY) and Agouti related Peptide (AgRP), two potent orexigenic peptides<sup>21</sup>. NPY promotes net energy gain by increasing food intake, decreasing energy expenditure and exerting effects in peripheral tissues, including stimulation of glucocorticoid and insulin secretion that favour deposition of triglycerides in white adipose tissue. AgRP is a 132 amino acid peptide, synthesized in the brain exclusively in the arcuate nucleus by neurons that project to the paraventricular nucleus and lateral hypothalamic area. AgRP's antagonism of the melanocortin 4 receptor stimulates food intake and decreases energy expenditure. A 17% diet induced weight loss leads to a 24% increase in plasma ghrelin levels indicating that ghrelin is at least partially responsible for the poor adherence to weight reducing diets<sup>22</sup>. The success of gastric bypass in maintaining weight reduction is consequently due in part to the very low ghrelin levels found in these patients<sup>22</sup>.

## HYPOTHALAMUS

From the above discussion it is clear that the hypothalamus is the central agency for integration of all the signals both neuronal and endocrine and maintaining the energy balance in the body. Neural impulses mostly vagal and hormonal signals in form of leptin, ghrelin, insulin, cholecystokinin all act on the hypothalamus along with metabolites like glucose. These diverse signals cause the release of the various peptides in the hypothalamus which modify both food seeking and energy expending behaviour. Orexin, melanin concentrating hormone (MCH), NPY and AgRP stimulate appetite whereas MSH and GLP-1 (Glucagon like peptide 1) would suppress appetite. This might be partially routed through the autonomic nervous system. In mice sympathetic activation of BAT is one of the methods of increased energy expenditure.

Another method of thermogenesis is the NonExercise Activity Thermogenesis (NEAT)<sup>23</sup>. NEAT is the thermogenesis that accompanies all the routine activities of daily life like walking, standing, fidgeting, posture maintenance etc., in short all activities apart from volitional exercise. If energy balance is ideal almost 70 percent of the extra energy expenditure on overfeeding is attributed to NEAT. The relative strength of induction of NEAT would determine to some extent the amount of extra energy leftover which would be stored as fat.

Lesions of the hypothalamus like tumours or inflammation can cause hypothalamic dysregulation resulting in obesity.

## HYPOTHALAMO-PITUITARY-ADRENAL AXIS

Central obesity is one of the hallmarks of Cushing's syndrome. Even though serum cortisol might be higher in obese patients, an overnight dexamethasone suppression test will be positive in an overwhelming 90% of patients thereby preventing confusion. The remaining 10% can be excluded on the basis of a 2 day low dose dexamethasone suppression test.

However more ominous is the permissive role of glucocorticoids in the development of central obesity in 'common' obesity (as opposed to those associated with specific disorders/mutations). The thrifty phenotype hypothesis suggests that in response to undernutrition, a foetus will selectively distribute nutrients to preserve brain growth at the expense of other organs such as liver, pancreas, and muscle<sup>24</sup>. The stress response to foetal undernutrition will lead to an increased ACTH secretion and a probable resetting of the HPA axis. As these individuals experience improved postnatal nutrition, the compensatory catch up growth is associated, as early 5yrs of age, with increased visceral adipose tissue and later with insulin resistance<sup>25</sup>. This might in part explain the explosion of obesity and diabetes in India and also the relatively higher incidence of diabetes in poor migrants from developing countries settling in urban centres/developed countries.

## STOMACH

The stomach plays an extremely important role in energy homeostasis, ghrelin release being only one of the mechanisms. Gastric distension and emptying play important roles in regulating food intake. Gastric distension with food relays a satiety signal to the hypothalamus through vagal afferents inhibiting further food intake<sup>26</sup>. Anorexigenic molecules like cholecystokinin not only suppress feeding on a hypothalamic level but also decrease gastric transit, thereby further inhibiting food intake<sup>27</sup>. On the other hand rapid gastric emptying is associated with overeating and obesity. Lesions of the ventromedial nucleus (VMH) of the hypothalamus result in disruption of autonomic control of the stomach causing an accelerated transit of food from the stomach<sup>28</sup>. As the stomach does not appropriately distend with food satiety signalling is defective resulting in overeating and obesity. This is thought to be the major cause of the obese VMH syndrome.

Leptin and its receptor have been identified in the gastric mucosa in humans<sup>29</sup>. Gastric leptin can be released into the blood and gastric juice after feeding, insulin-induced hypoglycemia, or infusion of CCK-8, pentagastrin, and secretin. Gastric leptin may have a role in appetite regulation by acting directly in the hypothalamus or in synergy with CCK via the vagal pathway or by modifying absorption of dietary protein and fats<sup>30</sup>.

Enterostatin, a derivative of procolipase (protein necessary for intestinal fat digestion) is also produced by the gastric chief cells. Enterostatin increases during fat feeding, where it is found in circulating blood as well as in intestinal lumen and the lymph<sup>31</sup>. Enterostatin inhibits gastric emptying and signals the hypothalamus as a satiety factor thereby reducing food intake.

## CONCLUSION

Multiple signals converge on the hypothalamus to regulate energy balance in the body. Knowledge of the molecular basis of the signalling will help modulate therapeutic measures to induce and maintain weight loss and prevent weight gain in the first place. However research into obesity has still a long way to go before translating into therapeutic measures.

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