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Insulin and human obesity

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Abstract

The prevalence of obesity among the modern communities increases dramatically and trends to achieve the characteristics of epidemic. Obesity is the result of sedentary life style and increased food intake, which characterises the Westernalized communities. Obesity is closely related to insulin resistance and hyperinsulinemia and the very frequent combination of obesity and NIDDM is characterised as "Diabesity". The behaviour of man in seeking food and the amount of food consumption is a complicated situation, which is regulated by the CNS and especially in the arcuate nucleus of hypothalamus. A repertoire of neurohormonal actions, generated in peripheral tissues and integrated in the CNS, encompass many peptides with orexigenic and anorexigenic action. Two main hormones, insulin and leptin, accomplish the fine - tuning of these peptides action, at the critical level of body weight and energy control. The high prevalence of insulin resistance and hyperinsulinemia in obesity indicates a causative relationship between these two situations. It seams likely that insulin resistance of muscle cells is the primitive "defect" which renders individuals vulnerable to obesity. The high prevalence of insulin resistance, about 25 %, among otherwise healthy subjects indicates that this genetically determined "defect" may be the result of an evolutionary selection, which rendered man's kind capable to survive under long periods of famine, during his long journey from the hunter-gatherer period of his life to the present time of plenty.

Introduction

Obesity is the new epidemic of the developed and developing countries all over the world as a result of increased food consumption and sedentary life style in the majority of the modern communities. According to the latest WHO data about 1 billion adults are overweight and about 300 million are obese[1]. The incidence of obesity is rapidly increasing the last two decades and there is no evidence to decline during the next decade. According to the data of the National Heath and Nutrition Examination Survey[2] (NHANES) during the period 1999-2000, conducted in USA population, 65 % of adults are overweight (BMI = 25-29,9 Kg/m2) compared to 47 % during the period 1976-1980 (NHANES II). The prevalence of obesity (BMI ? 30 Kg/m2) in the same population increased from 15 to 31 %. Unfortunately the same disappointing results are obtained among children population. About 17,6 million children, under age five, are estimated to be overweight woldwide[1]. Comparing the results of NHANES (1999-2000) and NHANES III (1988-1994) an increasing rate of overweight was established between ages group as follow: 12-19 years old 15,5 %, 6-11 years old 15,3 %, 2-5 years old 10, 4 % compared to 10,5 %, 11,3 % and 7,2 % respectively[3].

Key words: insulin, leptin, obesity, energy balance.

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Obesity and overweight constitute major risk factors for serious chronic diseases such as type II diabetes, cardiovascular disease, hypertension, stroke and certain forms of cancer, such as colon, breast, endometrium and prostate. The financial burden of obesity upon the health care costs of the developed countries vary between 2,6 - 7 % annually, although it may be underestimated[1].

Obesity is closely related to insulin resistance and hyperinsulinemia. The combination of obesity, hyperinsulinemia, hyperlipidemia and hypertension is referred to as "syndrome X", "deadly quartet" or "metabolic syndrome" and has been the subject of extensive investigation the last two decades, because of the violent influence upon the public health[4,5,6].

The coexistence of obesity and insulin resistance or hyperinsulinemia is well recognized7 and suggests the possibility of a causal relationship between these two abnormalities. The question is whether this coexistence is incidental or genetically determined and what is exactly the primary disturbance: obesity or insulin resistance?

Pathogenesis of obesity

Obesity is the most common disturbance of metabolism in man and is recorded about 10.000 years before the development of agriculture. It is the result of increased food intake and decreased thermo genesis with a resultant increase of fat accumulation in adipocytes. The adipose tissue is the main store of energy in mammals, in the form of esterified fatty acids, accumulated during periods of nutritional abundance in order to survive during famine. It is well now recognized that the human organism possess mechanisms which regulate food intake and energy storage during periods of food access which helped man to survive during his long journey since the hunter-gatherer period of his life until now[8,9]. Obesity seems to be the result of an ineffective action of these mechanisms, which are unable to stop the excessive food intake, under conditions of plenty. From a teleological point of view it is possible that the mechanisms counteracting the excess food intake are blunted as a result of an evolutionary selection because the major threat for human surviving, thousands years ago, was starvation and not the bounty of a modern buffet[10].

The energy balance and food intake in humans encompass a delicate network of neurohormonal actions generated in peripheral tissues and integrated in the central nervous system, mainly in the arcuate nucleus of hypothalamus, which regulate the behaviour to seek food and the metabolic pathways for the storage of energy excess[9].

These actions are divided in two pathways: The short-term appetite regulation and the long-term weight regulation. The first one is responsible for the immediate regulation of the behaviour to seek food and the quantity of food consumption and the second one for energy storage and regulation of energy disposal.

The first pathway encompasses orexigenic and anorexigenic peptides as well as afferent vagal stimulation to the hypothalamus. Known peptides with orexigenic action are the agouti related protein (AgRP), the neuropeptide Y (NPY) and ghrelin (Ghr). The anorexigenic peptides are the α-Melanocyte Stimulating Hormone (α-MSH), the Peptide YY3-36 (PYY) and the Cholecystokinin (CCK)[9,11]. (Table I).

Orexigenic peptides	Anorexigenic peptides
AgRP (blocks Rs of α-MSH)	α-MSH (↓ food intake - ↑ energy production)
NPY (↓ POMC gene expression)	PYY_{3-36} (↓ NPY and ↑ POMC expression)
Ghr (↑ AgRP and NPY)	CCK (↓ stomach emptying, fullness sensation, vagal stimulation)

Table I: Peptides implicated in energy balance and fat tissue mass.

AgRP antagonises the action of α-MSH at the level of its receptors (MC4-R and MC3-R). The NPY decreases the expression of gene encoding the synthesis of proopiomelanocortin (POMC), the precursor molecule of α-MSH. Ghr, which is produced by the oxyntic cells of stomach fundus, increases the production of NPY and AgRP at the level of hypothalamus. CCK is produced in the small intestine in response to dietary fat and slows the emptying of stomach, increases gallbladder contraction and produces a sense of fullness transmitted to the brain via afferent vagal stimulation. Peptide YY3-36, which is produced by the L cells of distal small bowel and colon, decreases gut motility and NPY expression and increases POMC expression in hypothalamic neurons.

The second pathway encompasses the α-MSH and its receptors, mainly the Melanocortin Receptors 4 and 3 (MC4-R, MC3-R), which regulate food intake and energy expenditure through interactions with orexigenic and anorexigenic peptides, at the level of hypothalamus, as well as with Thyroid Releasing Hormone (TRH)[12,13]. The action of α-MSH upon MC4-R is expressed as a decrease of food intake and an increase of energy production where as the stimulation of MC3-R is coupled mainly by energy disposition.

The action of these peptides is regulated, at the level of arcuate nucleus, by two hormones: Leptin and Insulin. (Figure: 1).

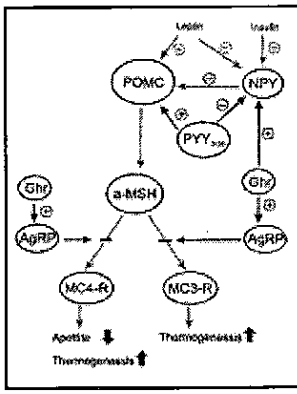

Figure: 1. Action of Insulin and Leptin, at the level of arcuate nucleus. Insulin inhibits NPY production, abolishing its inhibitory effect upon POMC synthesis. The net effect of this action is a decrease in appetite and an increase in thermogenesis, favoring the reduction of fat stores.

Leptin is the product of the ob gene of adipocytes[14] and insulin the product of islet β-cells of pancreas. The blood levels of these two hormones are proportional to the size of the adipose mass, so that in instances of adipose mass expansion insulin and leptin levels increase and exert a catabolic effect, in the opposite situation insulin and leptin levels decrease and produce an anabolic effect in attempt to achieve effective energy balance[15].

Insulin and leptin access the central nervous system crossing the blood brain barrier via specific, saturable, receptors at the level of capillary endothelial cells and cerebrospinal fluid concentrations parallel that of plasma. Intracerebral administration of insulin and leptin reduce food intake and body weight at a dose depended manner. Insulin and leptin exert their action via specific receptors, at the level of hypothalamus, which are expressed at the critical area of food intake and body weight regulation[15].

Neurons that are primarily affected by the intracerebral action of insulin and leptin are the POMC, NPY and AgRP expressing neurons. Insulin inhibits the expression of NPY in arcuate nucleus and leptin inhibits expression of NPY and increases expression of POMC8. Experiments in laboratory animals showed that specific disruption of insulin receptor gene in CNS produces insulin resistance, hyperleptinemia, obesity and hypertriglyceridemia[16].

The problem with these two hormones is that they are constantly increased in obesity and seems likely that obese individuals are not responsive to their action suggesting the presence of insulin and leptin resistance. Conversely if the obese individuals are deprived of the action of insulin and leptin, as it is truth during fasting, they exhibit an increase in food intake and energy accumulation. So we can infer that the action of these hormones is mainly to defend against fat and energy wasting.

Insulin resistance - Hyperinsulinemia and Obesity

Since the first description of the resistance to insulin stimulated glucose uptake in the forearm of obese subjects, by Rabinowitz and Zierler in 1962[17], numerous epidemiological studies have established the close relation between diabetes and obesity. The term "diabesity" has recently adopted and is characterized by the combination of obesity and insulin resistance or hyper-secretion. The explosive emerge of "diabesity", the last two decades, tends to achieve the characteristics of global epidemic with a tremendous impact upon the health care systems[18].

Insulin resistance is encountered in about 25 % of otherwise healthy subjects, and is characterised by a decrease in insulin-stimulated glucose uptake and metabolism by the skeletal muscle and adipose tissue and the inability to suppress hepatic glucose output. This defect of insulin action tends to increase blood glucose concentration and as a result the pancreatic β-cells increase insulin production in an attempt to compensate for insulin resistance. If hyperinsulinemia fails to overcome the resistance, of insulin sensitive tissues to glucose uptake, then diabetes is established[19].

It has to be emphasized that insulin resistance and hyperinsulinemia are not exclusive features of obesity and obese individuals does not exhibit a unique feature of insulin resistance and hyperinsulinemia. Careful examination of the database of the European Group for the Study of Insulin Resistance (EGIR) showed that about 10 % of lean, normotensive, individuals exhibited insulin resistance and hyperinsulinemia compared to about 26 % of all obese subjects. The prevalence of insulin resistance and hyperinsulinemia rise dramatically in obesity, according to the BMI, from 19 % for individuals with BMI < 30 Kg/m2 to 34 % with BMI < 35 Kg/m2 and individuals with BMI > 35 Kg/m2 exhibited a 60 % prevalence of insulin resistance and 80 % of hyperinsulinemia[20].

It is obvious that insulin resistance plays a key role in the pathogenesis of metabolic disturbances related to obesity and that obesity, per se, is capable to produce insulin resistance. Hence we have to consider the phenomenon of insulin resistance in more details and attempt to elucidate the defect(s), upon cellular level, which produce the defective insulin action.

Insulin exerts its metabolic action in glucose homeostasis upon the insulin sensitive tissues such as skeletal muscle, fat and liver. In skeletal muscle increases glucose uptake and storage in the form of muscle glycogen, in fat increases glucose uptake and formation of triglycerides and in liver decreases glucose output by inhibiting glycogen degradation. It is now known that under conditions of euglycemic clamp about 70 % of total glucose uptake occurs in skeletal muscle and only a little amount of glucose is up taken by fat tissue[19]. On the other hand adipocytes are the more sensitive cells to the action of insulin, which regulates almost all the aspects of their biology. Insulin promotes the differentiation of preadipocytes to adipocytes, increases the glucose uptake and triglycerides synthesis (lipogenesis) and inhibits lipolysis. The antilipolytic effect of insulin upon adipocytes is conserved even in case of insulin resistance, hence increasing the expansion of adipose stores. Insulin also increases the uptake of fatty acids, derived from circulating lipoproteins, by increasing the activity of lipoprotein lipase[21].

The metabolic action of insulin is initiated by coupling of insulin molecule with specialized receptors at the cell surface. Insulin receptors belong to the large family of growth factor receptors with intrinsic tyrosine kinase activity. Beyond the classic insulin sensitive tissues insulin receptors are located in many cell types all over the human body including CNS.

The coupling of insulin with its receptor activates the intracellular portion of the receptor, which acts as a tyrosine kinase and produce phosphorylation of multiple tyrosine residues in insulin receptor substrates (IRSs). Although a lot of IRSs have been recognized until now it is evident that most of insulin actions are mediated via two main IRSs, the IRS1 and IRS2. The IRS1 controls body growth and peripheral

insulin action, where as IRS2 controls brain growth, body weight, glucose homeostasis and female fertility[22].

The IRS proteins act as docking proteins for subsequent recruitment and phosphorylation of many other cytoplasmic proteins, which serve as substrates in the cascade of intracellular propagation of insulin signalling pathway. One of the most important substrate of IRSs proteins is the Phosphoinositide-3 Kinase (PI-3K), which catalyses the production of PI-3Pi from membrane lipid bilayers as well as from endoplasmic reticulum membranes. The activation of PI-3K is necessary for the initiation of events for the translocation of glucose transporter GLUT-4 from the cytosol to the membrane surface of skeletal muscle cells and adipocytes[23].

Protein Tyrosine Phosphatases, such as PTP-1B, catalyse the tyrosine dephosphorylation and inactivate insulin receptor substrates, disrupting the propagation of insulin signal upon the cell level. Experiments in laboratory animals showed that disruption of the PTP-1B gene rendered animals deficient of PTP-1B more sensitive to insulin action than the wild type and also more resistant to weight gain under high fat feeding conditions[24].

It is obvious that any defect in the cascade of these intracellular events is capable to disrupt the insulin signal and produce insulin defective action including insulin resistance.

On the other hand abnormalities of lipid metabolism, which accompany obesity, are capable to induce insulin resistance. Experimental data from humans and animals show that infusion of free fatty acids (FFA) induce diminished glucose uptake by muscle cells, which is consisted with insulin resistance[25, 26]. The underlying mechanism of this action is that FFA induces diminished phosphorylation of IRS-1 and PI-3K, as a result of increased intracellular concentration of Diacylglycerol (DAG), which increases the activation of PKC-θ isoform, a known serine kinase. Increased activation of PKC-θ leads to IRS-1 Ser307 phosphorylation, which in turn inhibits the phosphotyrosine-binding (PTB) domain of IRS-1. (Figure: 2).

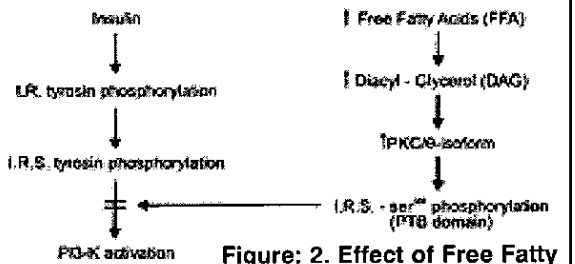

Figure: 2. Effect of Free Fatty Acids (FFA) upon Insulin signal propagation at the cellular level. FFA increase IRS-serine307 phosphorylation and produce PTB-domain inactivation.

Activation of the PTB domain is necessary for PI-3K phosphorylation and activation and subsequent migration of GLUT-4 to the cell membrane of skeletal muscle and adipocytes. The same intracellular pathway is activated by TNF-a, which produces also insulin resistance, so it is possible that FFA inhibits IRS-1 phosphorylation by a manner similar to that of TNF-a[26].

Current investigation, in attempt to identify the human obesity gene map, is growing rapidly but the results are disappointing because all human chromosomes are candidate harbors of obesity genes except chromosome Y. According to the tenth update of the human obesity gene map, more than 430 genes, markers and chromosomal regions have been associated or linked with human obesity phenotype[27].

Insulin resistance - fat stores and survival of man's kind

From all the above it is obvious that any aberration in insulin signaling cascade is genetically determined but environmental factors, such as FFA concentration, are capable to modulate the response of the cell to the insulin signal. The peculiar aspect of this statement is that genetic predisposition and environmental factors are targeted to the same end point: increase of body fat stores. From a teleological point of view we have to consider that human organism acts toward fuel storage beyond the instantaneous needs but with providence to the future needs.

James Neel, in 1962, postulated that the diabetes predisposed individuals are characterised by the presence of insulin "over-production" at some stage during food ingestion cycle. This, genetically determined, characteristic renders these individuals capable to handle a given glucose load better than the remainders and so gives the opportunity to store a greater amount of energy for later use during fasting[28]. The property of these individuals for more efficient handling of energy excess, during periods of feast, renders them more capable to survive during periods of famine, so may it is a characteristic which has been selected during the evolution of man kind from the hunter-gatherer period of his life until now. The modern man has the opportunity of excess food intake in every time, so his genome, which rendered him capable to survive in starvation periods, renders him today vulnerable to obesity and diabetes mellitus.

Under the light of knowledge that the principal characteristic of non insulin depended diabetes mellitus (NIDDM) is the muscle resistance to insulin action, Michael Wendorf and Ira Goldfine, in 1991, reassessed Neel's hypothesis and suggested that the advantage of individuals with muscle cells insulin resistance is the avoidance of hypoglycaemia, during starvation, with the ability to conserve glucose as fuel for neuronal tissues, and allow them to store all the available energy in fat tissue and liver during feeding[29].

The "thriftiness" of this genotype is that gives advantage for survival under conditions of scanty

food intake during the hunter-gatherer period of man evolution. Under conditions of free food access these individuals exhibit hyperglycaemia and hyperinsulinemia and accumulate all the energy excess in fat stores. They become obese with a resultant insulin resistance in fat tissue and liver, which predispose them to NIDDM.

As it was stated above the behaviour to seek food and the fat stores of the organism are closely related to the energy balance, therefore it is proper to seek a link between these items. What tells the brain that starvation is present and our body has to cope with it and what tells that excessive energy is accumulated and it has to spend it?

Jeffrey Flier, in 1998[10], attempted to give an answer to this question under the light of evidence after leptin discovery. It is now well known that leptin levels increase parallel to the increase of fat stores and decline rapidly during starvation. For a long period, after its discovery, it was considered as a lipostatic hormone, because in cases of leptin deficiency in humans, especially in young children with severe obesity, exogenous administration of the hormone gradually restored normal body weight[30]. In the majority of obese individuals leptin levels are increased and they are likely to exhibit resistance to the leptin action, but in the fasting state and especially in cases of fat tissue loss leptin levels decrease rapidly with a resultant decrease in thermogenessis and increase in appetite. Therefore it is unwise to consider that the evolutionary selection of this phenotype was relied upon the hormone resistance in obesity. It is more likely to accept that leptin deprivation acts as a switch in case of transition from fullness to starvation and alarms the brain toward seeking food and preservation of energy stores.

According to Flier's hypothesis in case of low leptin level and activity thermogenesis decreases and appetite increases, this combination leads to increased energy deposits and fat storage. As fat stores increase leptin level increases also and if the individual exhibits normal leptin activity appetite decreases and thermogenesis increases, favouring energy consumption and fat stores reduction but if leptin resistance is present leptin level increases without increase in leptin action so energy deposits and fat stores continue to increase leading to obesity.

It has to be emphasised that normal organism exhibit relative tolerance to energy deposits and fat storage because of the threat of starvation and the action of leptin is somewhat blunted favouring obesity than leanness, so we have to say that the obese man who likes to be lean has to fight against his genome.

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