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Review On: Obesity and Nutritional Disorder in Mammals

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Abstract: Obesity is formally defined as a significant increase in ideal weight, ideal weight being defined as the level at which life expectancy is maximized. A key element of animal and human obesity is the hormone leptin which acts on nerve cells in the brain to regulate feed intake and body weight. Obesity is a major risk factor for the development of type-2 diabetes and is an important obstacle to the management of this disease. It is a leading cause of human morbidity and mortality. The other hormone that plays a role in energy homeostasis of mammals is ghrelin. In addition to hormonal effect, the prevalence of obesity in mammals has been linked to insufficient maternal nutrition during gestation. This review explored the pathogenesis of obesity and other metabolic disorders in relation with the hormone leptin and ghrelin. In addition, we reviewed the impact of maternal nutrition during pregnancy to the development of obesity and type-2 diabetes and the possible options to modulate obesity and type-2 diabetes.

Key words: Adipose Tissue Programing · Anorexia · Ghrelin · Hyperphagia · Leptin · Maternal Nutrition · Obesity · Type 2 Diabetes

INTRODUCTION

Obesity is formally defined as "a significant increase in ideal weight, ideal weight being defined as the level at which life expectancy is maximized" [1]. Obesity has the tendency of increasing an animal's susceptibility to a range of diseases and physiological problems which are associated to lower life expectancy [2, 3]. Among the predisposing factors, several studies involving mammals have linked obese phenotypes to hormonal resistance [4] and restriction of maternal nutrient intake [2, 3]. Maternal diet during pregnancy is an important environmental factor influencing the growth and development of the fetus [5]. Recently, nutrition during gestation has also been postulated as an epigenetic contributor to health in adulthood, influencing bone health and weight status [6].

In addition to hormonal effects, the prevalence of obesity in mammals has been associated with insufficient maternal nutrition during gestation [7]. Neonates from undernourished mothers have shown to develop a number of metabolic disorders later in their life, for example hypertension, cardiovascular disease, type-2 diabetes and obesity [2, 3]. The occurrence of obesity and other metabolic diseases in mature offspring from undernourished mothers are largely due to disparities between the prenatal and postnatal environment from which they were born. Epidemiological and animal studies have determined that obesity and type- 2 diabetes are pathologies programmed by adverse events in utero or early postnatal life [8] therefore, it is unsurprising that adipose tissue is a prime target. The aim(s) of this review is to assess the effect of obesity and nutritional disorder in mammals.

Obesity and Type-2 Diabetes: A key element of animal and human obesity is the hormone leptin which acts on nerve cells in the brain to regulate feed intake and body weight [1]. Obesity is a major risk factor for the development of type-2 diabetes and is an important obstacle to the management of this disease [9]. It is a leading cause of human morbidity and mortality associated with type-2 diabetes, largely through its contribution to cardiovascular disease [9, 10]. Dietary energy sources are needed in excess for maintenance, growth; reproduction, lactation and work and heat production are stored as glycogen in the liver and as body fat stores. When fat stores are not utilized, a dietary-induced obesity and other metabolic diseases, such as type-2 diabetes can be developed [11].

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An imbalance in ingested energy as food and expended energy for physiological functions are the basic cause of obesity. According to Keenan *et al.* [10] "the excess energy is stored in fat cells that undergo hypertrophy and hyperplasia and become the initial pathological lesion in the obese individual. Enlarged fat cells produce clinical problems by their mass and increased secretion of free fatty acids (FFAs) to the liver that modulate the metabolism of insulin".

Obesity is largely the result of genetic factors [12]. Obesity genes encode the molecular component of the physiological system that regulates body weight. In humans, at least 17 genes are associated with obesity and 18 genes have been associated with type 2 diabetes [10]. In addition, epigenetic factors and intrauterine imprinting as well as some environmental and physiological agents are added risk factors [12]. But a positive energy balance in excess of essential caloric requirements is necessary to induce excessive storage of lipids in body fat and to induce a person or animal to become overweight and obese. Mutation in the leptin receptor is also associated with extreme obesity [4].

Obesity and type-2 diabetes are associated with a state of insulin resistance characterized by a reduced ability of insulin to exert its metabolic effects on key target tissues [9]. Insulin resistance could increase cancer risk through a chronic state of hyperinsulinemia, elevated levels of insulin-like growth factor (IGF-1), adipokines and other growth factors. Insulin is both a growth factor and a metabolic hormone and cancer cells often express insulin receptors, IGF-1 receptors and other growth factor receptors [11].

It has also been reported that excess energy intake contributed to obesity in rodents. In rodents, the excessive growth from caloric excess induces hyper secretion of pituitary prolactin and growth hormone that increases IGF-1 production that in turn induces systemic growth effects [13]. In addition, the *ad libitum* consumption of high fat diet changes body composition and metabolic status, resulting in diet-induced obesity and altered levels of cholesterol, triglycerides and insulin [2,14]. However, important genetic differences were observed in different mouse strains that fed the same high fat diet [12]. This might indicate that the pathogenesis of diet induced obesity is the result of an interaction between genetic, environmental and physiological factors.

Leptin and Development of Obesity: Leptin and ghrelin are two hormones that have been recognized to play an important role on energy homeostasis in mammalian species [15, 16]. Their involvement in the regulation of food intake and body weight is vital as voluntary feed intake of mammals is believed to be regulated by negative feedback mechanism to specific regions of the hypothalamus [17].

The adipose hormone leptin is an anorexigenic and acts in the hypothalamus to reduce appetite and increase energy expenditure in response to a meal in healthy animals [1,16].Obese animals have elevated leptin levels due to their greatly increased adipose tissue mass but are resistant to leptin's anorexigenic effects [1,10]. Increasing leptin levels which is associated with increased body fat results in a negative energy balance, whereas decreasing levels lead to positive energy balance (food intake > energy expenditure) [1,12]. Leptin reports the nutritional information to the key regulatory centers in a brain region known as hypothalamus; a decreased level stimulate food intake whereas increased level reduce feed intake. By such mechanism, weight is maintained within a relatively narrow range.

Leptin acts on nerve cells and modulates their function in the presence of brain peptides including neuropeptides Y (NYP) and agouti-related protein (AGRP), which stimulate food intake and α-melanocyte-stimulating hormone (α-MSH) and cocaine- and amphetamine-regulated transcript (CART), which decrease food intake [1]. Mutations in proopiomelanocortin (POMC), the precursor of α-MSH are associated with obesity. Mutation in the leptin receptor is also associated with extreme obesity [4].

The adipocyte specific hormone leptin, the product of obese (ob) gene regulates adipose tissue mass through hypothalamic effects on satiety and energy expenditure [18]. In human, leptin deficiency due to a mutation in the leptin gene is associated with early onset of obesity [4]. In obese human, high level of plasma leptin and/ or increased level of leptin RNA are indicative of leptin resistance [12]. However, a subset of obese human (5-10%) has relatively low plasma levels of leptin [12, 19], indicative of a reduced rate of leptin production in this subgroup. Abnormal regulation of the leptin gene in adipose tissue is etiologic in the pathogenesis of the obese state. A decreased leptin expression per adipocyte could lead to obesity with normal plasma leptin concentration [12]. This is observed in ob/ob mice carrying a poorly expressed leptin transgene; which are obese, despite having relatively normal leptin levels [18].

The role of leptin in the pathogenesis of obesity can be analyzed by measurement of plasma leptin level (Figure 1). According to Friedman and Halaas [12] there are three general mechanisms where alterations of the leptin regulatory loop could lead to obesity: **a** indicates

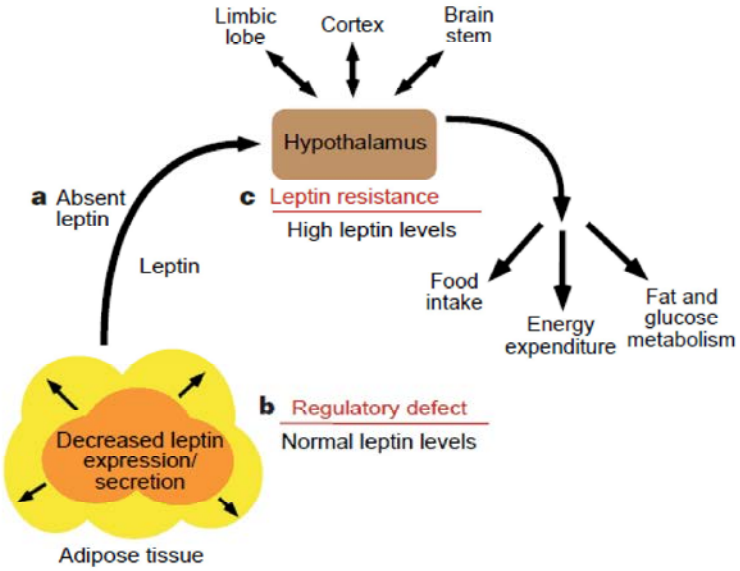

Fig. 1: Pathogenesis of obesity (Adapted from Friedman & Halaas, 1998 [12])

failure to produce leptin, as occurs in *ob/ob* mice would result in obesity, as would **b**, inappropriately low leptin secretion for a given fat mass. In the latter case, the fat mass would expand until 'normal' leptin levels are reached, resulting in obesity and **c** indicates obesity could result from relative or absolute insensitivity to leptin at its site of action. Such resistance would be associated with increased circulating leptin.

It has also been reported that changes in leptin concentration have effect on many organ systems including reproduction, the immune system and bone formation, which indicates that leptin is an important means by which changes in nutritional state affect physiology [12].

The Hormone Ghrelin: The other hormone that plays a role in energy homeostasis of mammals is ghrelin. Ghrelin, a 28 amino acid peptide with structural resemblance to motiline, was obtained in the stomach as an endogenous ligand for growth hormone secretagogue receptor (GHS-R) [20]. It is of two types: acylated and des-acyl ghrelin. Acylated ghrelin is involved in the regulation of growth hormone secretion, energy balance, gastrointestinal motility, cardiac performance and anxiety. Ghrelin is believed to functions as an orexigenic peptide in different mammalian species [21] and is involved in the hypothalamic regulation of energy homeostasis [22].

The pre-prandial release of ghrelin from the stomach has been linked with hyperphagia in mammals [20, 22]. Asakawa *et al.* [20] investigated the effect of des-acyl ghrelin using transgenic and non-transgenic mice and found that des-acyl ghrelin induced a state of negative energy balance and body weight loss by inhibiting food intake and delaying gastric emptying in inverse manner to acylated ghrelin. This is consistent with the effect of high level of plasma leptin on mammals [1]. Hence, the stomach may regulate energy balance through acylated and des-acyl ghrelin as an endocrine organ. A chronic intracerebroventricular (ICV) infusion of ghrelin (250 pmol d-1) for 12 days increased food intake and body weight gain in rats that are genetically deficient in growth hormone (Fig. 2). This indicate that ghrelin is involved in the release of growth hormone and it augmented NPY gene expression and blocked leptin induced feeding reduction, implying that there is a competitive interaction between ghrelin and leptin in feeding regulation.

On the contrary, De Smet *et al.* [23] reported that ghrelin is not an essential regulator of food intake and gastric emptying in ghrelin knockout and wild-type mice. But, the authors reported exogenous administration of ghrelin increased food intake in both genotypes. In addition, the primary orexigenic effect of ghrelin in old mice may be to function as an endogenous meal-initiating signal and this effect is triggered by the light/dark cue and ghrelin is likely to be involved in the preference of metabolic fuel oxidation and in the partitioning of metabolizable energy between storage and dissipation as heat, leading to an altered body composition.

Managing Type-2 Diabetes and Obesity: Obesity is the disequilibrium between energy intake and energy expenditure. Any factor lowering the energy intake would

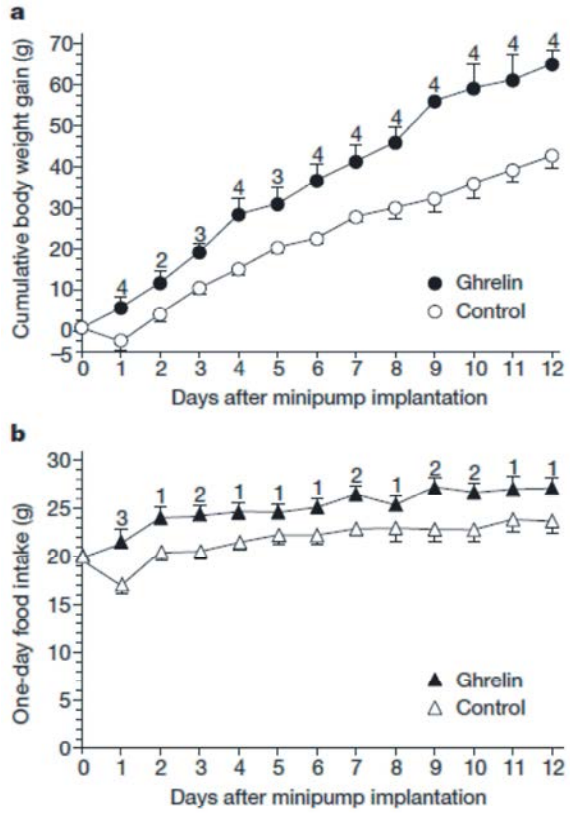

Fig. 2: Effect of chronic ghrelin ICV administration on rats. Cumulative body weight gain (a) and one-day food intake (b) during an ICV infusion of 250 pmol d-1 for 12 d (Adapted from Nakazato *et al.* [22]).

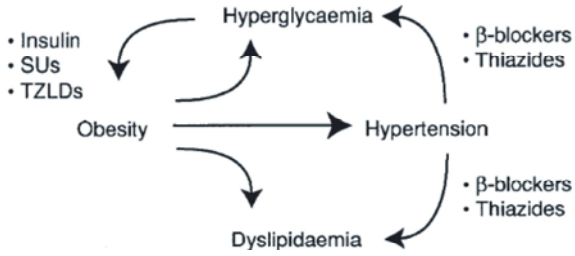

Fig. 3: Type-2 diabetes: a therapeutic `merry-go-round'. (SUs: sulphonylurease; TZLDs: thiazolidinediones) (Adapted from [9]).

have a profound effect in the regulation of energy homeostasis [16]. Type-2 diabetes can be managed by conventional approach using insulin and sulphonylurease but these two effective treatments frequently lead to weight gain (Figure 3). The side-effects and metabolic effects of drugs used to manage type-2 diabetes and obesity bring other complications. For example, controlling of blood glucose levels with insulin or sulphonylurea therapy, can lead to weight gain which in turn may worsen insulin resistance and other aspects of the metabolic syndrome, resulting hypertension and dyslipidemia. In addition, treating hypertension with the conventional combination of b- blockers and thiazides can exacerbate hyper-glycaemia and worsen dyslipidemia.

To overcome the aforementioned complications, body weight loss might be taken as an option. Body weight loss (5-10%) in obese patients with type- 2 diabetes can significantly improve their clinical condition. The multiple beneficial effects of weight loss on several features of the metabolic syndrome (that is insulin resistance, hyperglycemia, hypertension and dyslipidemia) that contributes to atheroma mean that weight reduction is a rational and conceptually attractive option in the management of type 2 diabetes [9]. The body weight loss can be obtained by moderate dietary restriction. It has been reported that 25 to 50% reduction in maximal adult food consumption (without malnutrition) consistently increases both mean and maximum life span of laboratory rodents and other animals by delaying the development of obesity, diabetes, renal, cardiovascular disease and cancer [10]. The authors expounded that dietary restricted animals, as compared to animals fed ad libitum, have a lower body weight, smaller skeletal size, decreased adipose tissue mass and decreased weight of most internal organs except for brain and testis. In addition, intraperitoneal administration of des-acyl ghrelin might contribute to body weight loss through its effect on reduced feed intake [20].

In utero and early postnatal nutrition programing plays a great role in the control of obesity and type-2 diabetes. Programming is defined as “a process through which exposure to environmental stimuli or insults during critical phases of development brings about permanent changes to the physiology or metabolism of the organism” [24]. The embryonic, fetal and early postnatal periods represent critical stages of development during which programming of body systems can occur. Thus, there is great potential for the in utero and early postnatal environment to impact on future physiological and biochemical systems, including adipose tissue [8].

Epidemiological evidence indicated that growth retardation in the fetal period, followed by catch-up growth in childhood is associated with cardiovascular disease, type-2 diabetes and obesity [3]. For example, Vickers *et al.* [2] reported that the restriction of maternal food intake to pregnant rats to just 30% of *ad libitum* produced marked hyperphagia and clear increases in adiposity in their offspring. When the offspring were

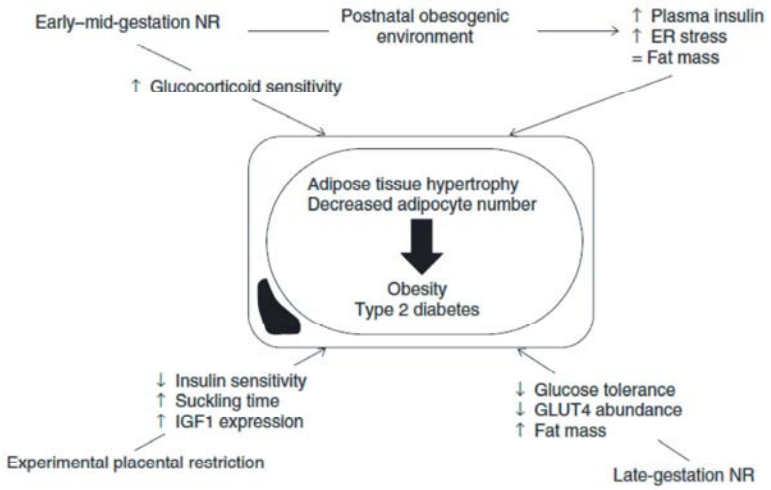

Fig. 3: Summary of adipose tissue programming effects in sheep subject to suboptimal in utero nutrition (either through dietary or placental manipulation) or a postnatal obesogenic environment in comparison with control animals. ↑, Increased; ↓, decreased; =, similar; NR, nutrient-restricted; ER, endoplasmic reticulum; IGF1, insulin-like growth factor 1(Adapted from [8]).

provided with high fat diet, they developed obesity. On the contrary, Bellinger *et al.* [25] fed pregnant rat low protein diet and found that prenatal under nutrition brought lifelong changes in feeding and locomotors behavior but has only limited influence up on long term patterns of fat deposition and obesity. However, this situation might be changed if the animals were challenged with a high fat diet in post natal life [25]. This might indicate that fetal under nutrition program results in high food intake postnatal and has contribution to incidence of obesity in the resultant offspring.

The effects of *in utero* nutrition in sheep were reviewed by Mostyn and Symonds [8]. Maternal nutrient restriction during late gestation in sheep at one year of age has resulted greater fat mass and impaired glucose tolerance, which is associated with a reduction in GLUT4 protein abundance in in adipose tissue. This result is complementary with the findings in human where late gestational nutrient restriction (NR) affecting intermediary metabolism (in particular glucose insulin homeostasis) and increasing the risk of the offspring developing type 2 diabetes. In addition, early –mid gestation NR and postnatal obesogenic environment (postnatal dietary challenge, reduced physical activity) play a great role in the development of obesity (Figure 2). Moreover, experimental restriction of placental growth resulted in reduced birth weight, increased early post natal growth and increased adiposity in the offspring at 6 weeks of age and impaired insulin sensitivity. This might indicate that intrauterine growth restriction might be a predisposing factor to obesity in later life. Early life programming of adipose tissue in sheep is presented in Figure 3. Therefore, prenatal programming of adipose tissue might have a profound effect in the control of obesity and type-2 diabetes.

CONCLUSIONS

The incidence of obesity in mammals can be attributed to leptin resistance and maternal nutrition during gestation. Although leptin is classified as an anorexic hormone, humans and rats displaying the obese phenotype have repeatedly shown to express high levels of leptin in the blood and brain. In addition, hyperphagia and increased body weight induced by mutations in the leptin gene sequence and genes for associated peptides has also been linked to the occurrence of obesity and type 2 diabetes. In addition, under nutrition during gestation has been observed to program tissues and organs of fetuses to function in a particular manner later in life.

The hormone ghrelin is also believed to play a role in energy homeostasis of mammals. It is involved in the release of growth hormone and it augments NPY gene expression and blocks leptin induced feeding reduction. This indicates that there is a competitive interaction between ghrelin and leptin in feeding regulation. Therefore, an increased understanding of these processes and the relative contributions of individual components of the diet to the endocrine

status of both the mother and resulting offspring will be important in improving the long-term health of mammals.

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