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CONCEPTUAL CONTRIBUTIONS

Regulation of energy balance and adiposity: a model with new approaches

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Obesity etiology and treatment have been fraught with disappointment for researchers, because the mechanisms regulating fuel homeostasis and adiposity are incompletely understood. It can now be hypothesized in the light of new evidences that the control of body weight and composition depends upon an axis with three interrelated and self-controlled components: 1) food intake; 2) nutrient turnover and thermogenesis and 3) body fat stores, all of which underly complex feedback mechanisms. This approach considers two of the most relevant recent findings in the field (leptin and β_3-adrenoceptors), adding new views to previous metabolic models of obesity. This perspective supplies some additional clues to the understanding of body composition regulation as well as the potential involvement of genetic and hypothalamic disorders in the onset of obesity.

Key words: Food intake (appetite), Nutrient turnover, Thermogenesis, Obesity, Leptin, β_3-adrenergic agonists.

The statement that obesity results from an imbalance between energy intake and energy expenditure is widely documented as well as the involvement of obesity in different health problems such as hypertension, hyperlipidemia, cancer, diabetes and cardiovascular diseases (9). However, obesity etiology and treatment have been fraught with disappointment, in part because the mechanisms regulating fuel homeostasis and adiposity are incompletely understood.

A vast amount of information concerning the control of body weight and composition has been published due to the discovery of the *ob* protein, also termed leptin (21). New scientific evidences have

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given a boost to the long time cherised theory that body fat content was regulated by a specific mediator (20). Thus, the common belief that obesity results simply from overeating or from a sedentary lifestyle has to be reconsidered. In this context, several investigations have been carried out both to establish the factors and situations affecting *ob* protein expression and to study leptin's physiological effects and regulation.

The *ob* protein is assumed to regulate body weight and fat deposition through effects on appetite as well as on metabolism and thermogenesis (10, 12). Serum leptin concentrations have been correlated with the percentage of body fat, which suggests that most obese persons are insensitive to endogenous ob protein (5), provoked by alterations in leptin receptors. However, these observations deserve further research for a deeper understanding (13, 18).

Other studies concerning physiological functions of leptin have revealed transient increases in ob gene expression after food intake (19), while evidence exists for a resistance to leptin action in animals fed high fat diets (8). Furthermore, both insulin and glucose have been shown to play a stimulatory role in ob gene expression in experimental animals (11), whereas fatty acids exert a concentration-dependent inhibition of leptin transcription in cultured adipocytes (14). On the other hand, results from time-course experiments have demonstrated that in adipose tissue *ob* gene expression is rapidly induced by glucocorticosteroids (6), while in adipose cells a marginal inhibitory effect of dexamethasone on leptin mRNA levels have been found (14).

Moreover, leptin as a sensor of fat deposition may be affected by β-adrenergic agonists, which may attenuate the overexpression of the ob gene in some experimental obesity models(4). Furthermore, an increased sympathetic outflow in response to leptin may be involved in the weight reducing effect of leptin by signalling the SNS to increase thermogenesis (3). Thus, research devoted to the study of the role of β_3-adrenergic compounds on the regulation of fat metabolism and their potential in the treatment of obesity, reveals its participation in fat cell function and lipolysis (1), which may be linked to leptin's mechanism of action (4).

In addition, neuropeptide Y, an appetite stimulating hypothalamic peptide, may have a crucial role as an effector of the leptin action, since one mechanism by which the ob protein could regulate food intake and metabolism is through inhibition of neuropeptide Y synthesis and release (15).

In this context the proposal of a new model for the regulation of body weight and adiposity is warranted because in the face of fluctuating food intake and energy expenditure, the precision (within ± 1% over many years) of body fat regulation requires a powerful, slow feedback pathway controlling total fat mass (15). Maintenance of the fat balance has assumed far less biologic importance, because the body's fat stores are too large to be markedly affected by daily imbalance in energy intake. However, sustained imbalance between the amount of energy consumed and the amount spent in everyday life certainly contributes to obesity onset. Nevertheless, other factors are influencing the energy balance equation such as macronutrient composition of the diet, distribution of energy expenditure and substrate homeorrhesis.

In the light of this new evidence, it can be hypothesized that the control of body weight and composition depends upon an axis with three interrelated and self-controlled components: 1) food intake; 2) nutrient turnover and thermogenesis and 3) body fat stores. All three elements underly complex feedback mechanisms (fig. 1).

Food intake elicits different sensory signals, gastrointestinal signals mediated by distension or local hormones, and

nutrient signals, which in turn, modulate appetite through specific mechanisms involving different neurotransmitters including monoamines (i.e., epinephrine, norepinephrine, dopamine and serotonin), amino acids (e.g., tryptophan, thyrosine and GABA) and neuropeptides (like pancreatic polypeptides, hormone-releasing factors, and diverse gut-brain peptides such as cholecystokinin and neuropeptide Y). The autonomic nervous system as well as several circulating hormones (insulin, cortisol, GH, etc.) are also involved in the metabolic response to food intake. All these signals, originating from food intake, generate neural as well as humoral outputs that trigger the appropriate quantitative and qualitative adjustments in intake, but also in the metabolism of energy and nutrients (2) through specific or unspecific mechanisms. Thus, glucostatic, lipostatic and aminostatic theories would not explain sufficiently this regulatory process.

A second loop would be constituted by the control of substrate cycling and thermogenesis, which not only depends on food supply, but also on specific mechanisms affecting the fuel mixture oxidized through efferent nervous, endocrine and enzymatic regulatory phenomena. The fat balance is poorly regulated as compared to protein or carbohydrate oxidation after food intake (7). The thermogenic state of the brown adipose tissue (BAT) results from a balance between influences of central origin and the sympathetic innervation of BAT (16). The outcome of this equilibrium has a direct influence on fat deposition as well as on food intake.

Finally, the role of the recently discovered leptin would cover the third regulatory system -a lipostat- informing about current stores to a central controller, which modulates fat deposition by triggering efferent nervous and endocrine signals mediated by β_3-adrenergic receptors and some homeorrhetic hormones or

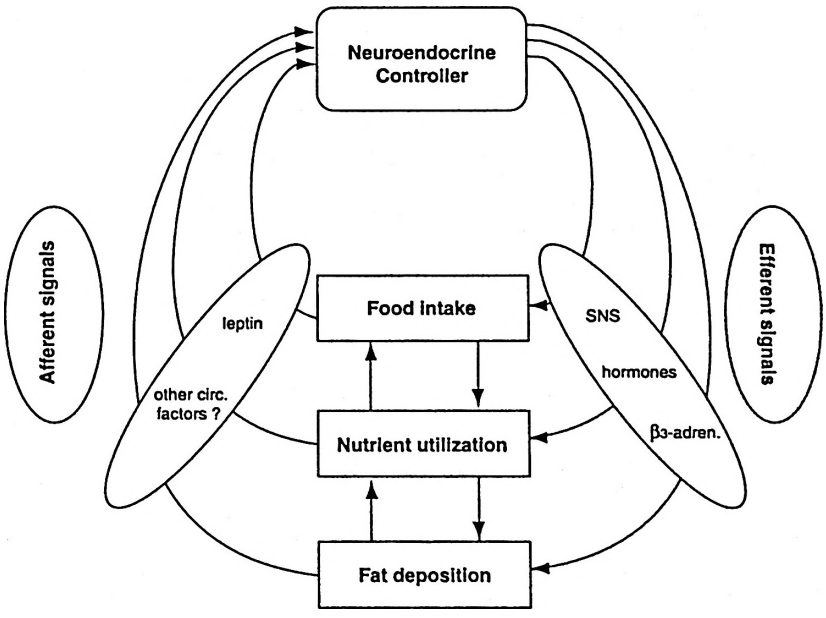

Fig. 1. *Schematic representation of the suggested hypothesis of body weight and composition control.*

peptides such as GH, IGF-I, insulin and adrenal steroids with direct effects on lipid turnover (2, 17). Adiposity, in turn, may affect directly or indirectly nutrient utilization and fuel selection.

This model supplies some additional clues to understand the precision of the body weight and composition regulation and the potential involvement of genetic and hypothalamic disorders on the onset of obesity rather than gluttony or sloth as formerly suggested. Furthermore, it also supports the development of new therapeutical strategies based upon the consideration of obesity as a chronic disease, which could be similar to the treatment of hypertension and in which dietary energy content, but also fuel distribution could be important. Undoubtedly, any integrative approach trying to explain obesity must consider the organism as a whole and take into account the myriad of complex physiopathological, psychic and social elements involved in its development.

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El estudio de la etiología y tratamiento de la obesidad resultan desalentadores para los investigadores, debido a que los mecanismos reguladores del balance energético y de los depósitos de grasa corporal no son plenamente conocidos. Algunas nuevas evidencias científicas permiten formular la nueva hipótesis de que el control del peso y de la composición corporal dependen de un eje con tres componentes íntimamente relacionados entre sí. Estos elementos son: 1) ingesta; 2) metabolismo de nutrientes y termogénesis así como 3) depósitos de grasa corporal; todos ellos sujetos a complejos mecanismos de retroalimentación. El enfoque planteado considera dos de los más relevantes hallazgos en el campo de la obesidad (la leptina y los receptores adrenérgicos β_3), además de añadir nuevas perspectivas a modelos metabólicos anteriormente establecidos del desarrollo de la obesidad. El planteamiento presentado proporciona información adicional respecto al conocimiento de la precisa regulación del peso y de la composición corporales, así como de la posible participación de alteraciones genéticas e hipotalámicas en la instauración de la obesidad.

Palabras clave: Ingesta (apetito), *Turnover* de nutrientes, Termogénesis, Obesidad, Leptina, Agonistas β_3-adrenérgicos.

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