Energy homeostasis and body weight in obesity: New physiopathological and therapeutic considerations

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ABSTRACT. This paper reviews recent developments and findings regarding the role of the hypothalamus as the main site in the central nervous system (CNS) for regulating appetite. It contains a specific neural network consisting of the main central monoaminergic neurotransmitters (adrenaline, noradrenaline, dopamine, serotonin) and many neuropeptides with orexigenic and anorexigenic functions. The crucial relationship between CNS and obesity and the complex interconnections of CNS and peripheral peptides are becoming clearer. The mechanisms by which these hormones affect energy homeostasis through long and short-term anabolic and catabolic pathways are described. New anti-obesity therapeutic strategies based on drugs or molecules with new mechanisms of action, some not yet available in Italy but will soon be on the market, are considered.

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INTRODUCTION

Obesity is a multifactor syndrome with excessive accumulation of fatty tissue as an expression of the volume and number of adipocytes. It is defined as chronic and excessive energy intake in relation to energy expenditure (Fig. 1). The simplicity of this equation hides a series of systems and interconnections which finely regulate the balance between energy intake and caloric expenditure, so that the total quantity of body tissue is always kept between a rigidly controlled range (1). Apart from the problems inherent in impaired energy expenditure, it is commonly accepted that even a transient increase in appetite leads to an increase in body weight. Specifically, there is a growing consensus that the expression of appetite is chemically coded in the hypothalamus, so that any environmental, genetic or hormonal alteration of the neurochemical signals at this level causes eating disorders such as hyperphagia or anorexia (2). Observations of this type have led to the identification of a complex neuronal pathway which involves the classic monoaminergic cerebral neurotransmitters (adrenaline, dopamine, serotonin), many cerebral nuclei and a large number of neuropeptides that regulate the drive to eat, consumption and utilization of food and thus maintain a proper rate of energy reserve in adipose tissue (3). The regulation of these factors is complex and consists of different signals that act simultaneously and are fundamental in maintaining energy homeostasis and body weight.

ENERGY BALANCE AND BODY WEIGHT

A significant number of nuclei in the basal hypothalamus are now recognized as crucial in the central regulation of energy homeostasis. Historically this homeostasis was attributed to a few neurotransmitters such as adrenaline, noradrenaline, serotonin and dopamine.

Adrenaline (A) and noradrenaline (NA) microinjected into the paraventricular nucleus (PVN) bind to the α2 adrenergic receptors located in this area of the hypothalamus, so that any environmental, genetic or hormonal alteration of the neurochemical signals at this level causes eating disorders such as hyperphagia or anorexia (2). Observations of this type have led to the identification of a complex neuronal pathway which involves the classic monoaminergic cerebral neurotransmitters (adrenaline, dopamine, serotonin), many cerebral nuclei and a large number of neuropeptides that regulate the drive to eat, consumption and utilization of food and thus maintain a proper rate of energy reserve in adipose tissue (3). The regulation of these factors is complex and consists of different signals that act simultaneously and are fundamental in maintaining energy homeostasis and body weight.

Key words: Obesity, neuropeptide Y, leptin, GLP-1, sibutramine.
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sion and thus inducing peripheral vasoconstriction. These effects are found even during the intake of α2 agonistic drugs (pharmacological agents) such as clonidine or molecules inhibiting NA reuptake (4, 5). The central action of catecholamines is also counteracted by dopamine (DA). When injected into the hypothalamus, DA binds to the δ2 receptors of the lateral hypothalamus and reduces food intake, in particular foods rich in proteins and lipids. DA agonists thus inhibit food ingestion, in contrast to the δ2 antagonists, such as sulpiride, which exert opposite effects (6, 7) (Table 1).

It is now well known that the serotoninergic system regulates eating behaviour. Serotonin (5-HT) binds to 5HTC2 receptors in the PVN and causes a decrease in food consumption. Studies in transgenic rats lacking 5HTC2 receptors confirm impaired feeding behaviour, with consequent development of obesity (8, 9). Drugs used in the pharmacological treatment of obesity thus modulate the balance between A and 5-HT.

The importance of monoaminergic cerebral neurotransmitters has been revised in light of evidence of many hypothalamic sites: the ventromedial nucleus (VMN), the dorsomedial nucleus (DMN), the PVN and the lateral nucleus (LH), which act in the regulation of feeding behaviour.

This new view is based on the results of numerous studies in which specific areas of the rat hypothalamus were bilaterally disrupted or specific neural pathways were surgically transected (10).

The VMN is regarded as the “satiety centre”. It shifts the metabolic energy balance in a catabolic direction with loss of body weight; it blocks liposynthesis in the adipose tissue, disperses energy by activating the sympathetic nervous system and inhibiting the vagus, thus increasing thermogenesis. Specifically, its disruption induces an increase in appetite with concomitant insulin hyperincretion and obesity (11). Bilateral disruption of the ventrolateral area produces opposite results. This area is recognized as the “appetite centre” because its stimulation induces an increase in caloric intake and shifts the energetic balance towards an anabolic direction (12).

The PVN oversees the regulation of ingestive behaviour by receiving signals elaborated in other CNS sites regulating vision, smell, hearing and circadian biorythms. An important role is also played by some nuclei located in the medulla oblongata, such as the dorsal motor nucleus of the vagus and the tractus solitarius which seems to be correlated to signals indicating the presence of food in the oral cavity or in other parts of the digestive tract.

From the integration at the hypothalamic level of short-term peripheral signals, indicating whether or not food is tasty, with long-term signals indicating the amount of fatty tissue, new responses regulated by the vegetative nervous system maintaining a constant body weight are issued (3).

The arcuate nucleus (ARC) is located at the base of the hypothalamus on either side of the third cerebroventricle.

This site has recently been thought to be

![Figure 1: Role of energy balance in the cause and origin of obesity.](image-url)