SUMMARY - Obesity results from a chronic imbalance between energy intake and energy expenditure. However, the biological mechanism(s) underlying possible alterations of energy balance is(are) still poorly defined. Advances in the understanding of body weight regulation in humans are represented by the discovery of: a) metabolic risk factors of body weight gain (i.e. low resting energy expenditure, low level of physical activity, high carbohydrate-to-lipid oxidation rate); b) the role of the autonomic nervous system in the control of energy metabolism and nutrient partitioning; and c) leptin, a previously unknown hormone produced by the adipocyte which seems to be quite involved in the complex neurohormonal regulation of energy balance. In view of these discoveries, current models of human body weight regulation concord on the existence of crosstalks between central nervous system and peripheral tissues. The brain monitors the nutritional status of the body (using several peripheral afferent signals including leptin) and reacts to nutritional changes by modulating the activity of its neurohormonal efferent signaling systems (autonomic nervous systems and endocrine organs). A low sympathetic nervous system (SNS) activity and a relative plasma leptin deficiency have been shown to predict body weight gain. Furthermore, plasma concentration of leptin and activity of the SNS seem to regulate each other. This paper reviews the evidence that previously described metabolic risk factors of body weight gain (i.e., low resting energy expenditure, low level of physical activity, and high carbohydrate-to-lipid oxidation rate) may in fact be the phenotypic expression of a dysfunctional leptin-SNS activity body weight regulatory loop.

Key-words : body weight gain, obesity, risk factors, leptin, sympathetic nervous system, regulation.

RÉSUMÉ - De la physiologie à la neuroendocrinologie : une réévaluation des facteurs de risque de la prise de poids chez l’homme. L’obésité résulte d’un déséquilibre chronique entre l’absorption et la dépense d’énergie. Toutefois, les mécanismes biologiques soutenant les altérations possibles de cette balance énergétique sont toujours mal définis. Un progrès dans la compréhension de la régulation du poids chez l’homme a été fait grâce à la découverte : a) des facteurs de risque métaboliques de la prise de poids (c.a.d. une faible dépense énergétique basale, une activité physique réduite, une forte transformation oxydative hydrates de carbone-lipides), b) du rôle du système nerveux autonome dans le contrôle du métabolisme énergétique, et c) de la leptine, hormone produite par les adipocytes et qui semble impliquée dans la régulation neurohormonale complexe de la balance énergétique. Au vu de ces découvertes, les modèles de régulation du poids corporel chez l’homme suggèrent tout l’existence d’inter-relations entre le système nerveux central et les tissus périphériques. Le cerveau intègre l’état nutritionnel corporel (grâce à différents signaux périphériques afférents, incluant la leptine) et réagit aux changements nutritionnels en modulant l’activité de ses systèmes neurohormonaux efférents (système nerveux autonome et organes endocrines). Une faible activité du système nerveux sympathique (SNS) et une carence relative en leptine plasmatique peuvent prédir une prise de poids. De plus, la concentration plasmatique de leptine et l’activité du SNS semblent se réguler mutuellement. Cet article analyse les données montrant que les facteurs de risque métaboliques de la prise de poids, cités ci-dessus, pourraient en fait constituer l’expression phénotypique d’un dérèglement de la boucle de régulation du poids corporel établie entre la leptine et le SNS. Diabetès & Metabolism 1998, 24, 108-115.

Mots-clés : prise de poids corporel, obésité, facteurs de risque, leptine, système nerveux, régulation.
he prevalence of obesity is increasing dramatically throughout the world in parallel with industrialization. It is estimated that 1 in 3 Americans is overweight or obese [1]. The health complications of obesity, such as diabetes mellitus, hypertension, hyperlipidaemia, coronary heart disease, and stroke, are major health problems and are consuming an increasing amount of health care resources [2]. In 1986, the US public health cost related to obesity was 36 billion dollars [3].

Obesity results from a chronic disruption of energy balance. The energy balance equation states that energy stores are dependent on the relative proportions of energy intake and energy expenditure. Energy intake is dependent on food consumption, while total energy expenditure can be broken down into 3 major components: resting metabolic rate, thermic effect of food, and the energy cost of physical activity. While food intake has been shown to be difficult to measure in humans [4], all components of energy expenditure can be accurately measured in a respiratory chamber [5], and physical activity by using the doubly-labeled water technique [6].

Studies of energy intake and energy expenditure in humans have helped in understanding that obesity is not only the result of bad behaviour (the so-called “sloth and gluttony” theory) but in many cases of inherited metabolic characteristics combined with unfavourable environmental conditions such as constant access to energy-dense food and minimal physical demands of daily living. Ravussin [7] has recently defined this as “pathoenvironment”, a provocative concept which calls for a cure of the environment rather than the people living in it. Because obesity has been increasing steadily in industrialized countries for the past 3 decades [1], and is now very common in populations migrating to westernized countries from countries with a traditional lifestyle [8], the negative impact of the pathoenvironment on body weight regulation is quite evident. However, obesity has long been known to be a familial disorder [9], and adoption and twin studies indicate that a significant proportion of the variability in body size and body composition is attributable to genetic factors [10, 11]. Furthermore, in populations like Native Americans and Pacific Islanders, obesity is far more prevalent than in any other population in the world [12, 13]. The challenge that we face is, therefore, to uncover the gene(s) and the encoded protein(s) that regulate energy intake and energy expenditure and make some individuals/populations more vulnerable than others to the deleterious effect of the pathoenvironment.

This paper reviews the experimental evidence that body weight gain in humans is predicted by metabolic risk factors such as a low resting metabolic rate (RMR), a low spontaneous physical activity and a high respiratory quotient, and evaluates the possible role of sympathetic nervous system (SNS) activity and leptin deficiency in causing alterations of energy metabolism leading to obesity. The role of the SNS and leptin in the regulation of food intake is not the focus of this paper, and the reader is referred to other reviews available on this topic in the literature [14, 15]. For the scope of this presentation, it should suffice to mention that both a low SNS activity and hypoleptinaemia have been shown to favour hyperphagia [14, 15].

**METABOLIC PREDICTORS OF BODY WEIGHT GAIN**

Cross-sectional studies of obese and lean individuals have revealed associations between various metabolic factors and obesity, but these relationships cannot be interpreted as causal. In contrast, longitudinal studies can identify predictors or risk factors for body weight gain and come one step closer to identifying cause-effect relationships. Since 1982, a population of Pima Indians living 50 miles south of the main metropolitan area has been followed up on a yearly basis at the research facility of the National Institutes of Health in Phoenix, Arizona [16]. This clinical longitudinal study was designed to identify risk factors for the development of type 2 diabetes and obesity. Several metabolic predictors of body weight gain have been identified: a low metabolic rate, a low level of spontaneous physical activity, and a high respiratory quotient [17].

RMR comprises 50-80% of daily energy expenditure. A sibling study in Pima Indians found that RMR aggregates in families, thus indicating that genetic factors underlie some of its interindividual variability [18]. A significant proportion of the remaining variability in RMR is related to differences in fat free-mass, fat mass, age and sex [19]. However, even after all the above variables are accounted for, RMR still differs markedly among individuals, and at any given body size one can have a high, normal, or low relative RMR. Among adult Pima Indians, those individuals with a low relative RMR are at approximately 8 times the risk of gaining 10 kg of body weight compared to those with a high RMR [20] (Fig. 1). These results have been confirmed in other populations [21, 22].

Spontaneous physical activity (or fidgeting) is the form of physical activity that is mostly unrelated to volition. It can be measured in a respiratory chamber using a radar system and is quantified as the percentage of time subjects are active while living in a restricted environment. Spontaneous physical activity varies widely among individuals, and it seems to be the most familial trait measured in a respiratory chamber, with family membership accounting for 57% of its variance [23]. In males, spontaneous physical activity correlated negatively with the rate of subsequent weight gain [23]. Because physical activity is expected to be much higher in free-living conditions...
than in a respiratory chamber, these results need to be confirmed in studies using doubly-labeled water. However, it is evident that the prevalence of obesity always parallels the decrease in the general level of physical activity in many populations.

Growing evidence indicates that the composition of nutrient intake and nutrient oxidation are also important factors in the genesis of obesity. The respiratory quotient, an index of the ratio of carbohydrate to fat oxidation, is also quite variable among individuals, even after adjustment for its major determinants, i.e. energy balance, adiposity and sex [24]. This indicates that some individuals are characterized by low fat oxidation rates and/or by the inability to increase fat oxidation in response to nutritional challenges. These metabolic characteristics also seem to be genetically inherited [24]. Among Pima Indians, those at the 90th percentile for respiratory quotient (carbohydrate oxidizers) had twice the risk of gaining 5 kg or more of body weight than those at the 10th percentile (lipid oxidizers) [24]. The activity of key enzymes of intermediate metabolism such as lipoprotein lipase (LPL), β-hydroxy acyl CoA dehydrogenase (β-OAC), and acetyl-CoA carboxylase (ACC) may underlie the genetically determined variability in respiratory quotient. LPL, plays a pivotal role in partitioning lipoprotein-borne triglycerides to adipose (storage) and muscle (mostly oxidation) tissues [25]. At rest, fatty acid oxidation accounts for 80% of muscle substrate oxidation [26]. Muscle LPL is the rate-limiting enzyme hydrolyzing lipoprotein-borne triglycerides to glycerol and fatty acids, which in turn enter the tissue through the endothelia-luminal interfaces of the capillaries [27]. Ferraro et al. [28] found an inverse correlation between muscle LPL activity and respiratory quotient in 16 Pima Indians and concluded that some of the interindividual differences in substrate oxidation are associated with differences in muscle LPL activity. β-OAC, another key muscle enzyme in fatty acid beta oxidation, was found to be related to whole body fat utilization. In a study of 14 Pima Indians, a negative correlation between respiratory quotient and the activity of muscle β-OAC was found, suggesting that a reduced capacity for fat oxidation in skeletal muscle is accompanied by a high carbohydrate-to-fat oxidation rate in the whole body [29]. It has recently been suggested that malonyl-CoA is a component of a fuel-sensing and signaling mechanism that responds to changes in fuel availability [30, 31]. The entry of acyl-CoA (derived from circulating FFAs or endogenous complex lipids) in the mitochondria where it is oxidized to acetyl-CoA, is controlled by malonyl-CoA, which synthesizes malonyl-CoA, may therefore represent a key enzyme in the regulation of nutrient partitioning and underlie some of the differences in lipid metabolism observed among individuals.

The 3 metabolic risk factors described above share some common characteristics. They are all familial traits and show a similar pattern in response to body weight gain. Relative to body size, low metabolic rate, low spontaneous physical activity, and high respiratory quotient predict body weight gain. However, with weight gain the metabolic rate and energy cost of spontaneous physical activity increase, whereas the respiratory quotient decreases. In other words, these risk factors tend to become ‘normal’ after weight gain, thus suggesting that their role in promoting body weight gain progressively decreases as obesity develops [17]. Further studies are needed to investigate whether or not these metabolic risk factors of body weight gain cluster in the same individuals and have an additive effect on body weight gain.

**SYMPATHETIC NERVOUS SYSTEM (SNS)**

The SNS and the adrenal medulla represent major physiologic regulators of body homeostasis. The SNS regulates the cardiovascular system and blood pressure by controlling both cardiac output and vascular resistance. The SNS also has an important role in regulating body temperature, some digestive secretions in the gastrointestinal tract, respiratory function and pupillary dilation. Finally, the SNS has effects on endocrine organs such as the pancreas and the adipose tissue, thus affecting fuel partitioning and mobilization.

Animal studies strongly suggest that low SNS activity predisposes to and is associated with obesity. In rodents with hypothalamic obesity (lesion of the ven-
tromedial nucleus), the firing rate of sympathetic nerves to brown adipose tissue is reduced in the basal state [32] and in response to nutritional challenges [33] and/or exposure to cold [32]. SNS activity is also low in genetically obese rodents (ob/ob mouse and fa/fa rat), resulting in decreased energy expenditure and increased food intake [34, 35]. In contrast, large inconsistencies are found in the literature when the activity of the sympathoadrenal system is compared in lean and obese humans. Two reviews of the numerous studies performed between 1980 and 1995 [36, 37] indicate that adrenal medullary function is probably reduced in obese subjects, whereas the relationship between SNS activity and obesity is unclear. Such inconsistency in the findings can be partially attributable to differences in experimental design, subject selection, and SNS measurement techniques. Many factors other than obesity may in fact contribute to the variability in SNS activity. These include gender, age, antecedent diet, blood pressure, glucose tolerance, physical activity and body fat distribution. Indirect measurements of SNS activity (R-R interval, pupillometry) originally indicated that obese subjects have depressed SNS activity [38]. Despite the wide scientific recognition of such findings, a series of more recent studies has shown, through direct measurement by microneurography, that SNS activity was increased in direct proportion to body fat [39-41]. As previously mentioned, cross-sectional studies are of little value in understanding the role of the SNS/adrenal medullary function in the aetiology of obesity since they cannot indicate whether differences in sympathoadrenal activity are the cause or the result of the obese state. To really understand the role of SNS activity in obesity, it is necessary to study it before weight gain, i.e. in pre-obese subjects. We have recently reported in a longitudinal analysis that low SNS activity is associated with body weight gain and development of central adiposity in Pima Indians [42] (Fig. 2).

**LEPTIN**

The recent discoveries of the obesity gene (ob) in the ob/ob mouse [43], its human analogue (OB), and its product, leptin [44-46], have shed new light on the relationship between adiposity and the hypothalamic regulation of energy balance and reproductive function [47, 48]. Leptin, a hormone secreted by the adipocyte, plays an important role in body weight regulation in rodents [44-46]. In the ob/ob mouse, obesity results from a genetic mutation that prevents the production of leptin by the adipocyte [43]. When administered to ob/ob mice, and at higher doses to normal mice, recombinant leptin decreases food intake [44] and increases body temperature [45], metabolic rate [45], and physical activity, resulting in a decline in body weight [44-46]. Leptin may act as a signal between adipose tissue and the brain (where leptin receptor is mostly expressed in the choroid plexus and hypothalamus [49]). In humans, leptin is secreted by the adipose tissue in proportion to the degree of adiposity [50, 51]. This has suggested that, in analogy with diabetes and insulin resistance, obesity may be considered as the phenotypic expression of leptin resistance or "functional" hypoleptinemia.

There is, however, considerable variability in leptin concentrations among individuals with comparable degrees of obesity [50], indicating that other factors influence plasma leptin concentrations. It is not clear whether hormones such as insulin and cortisol, which also participate in the regulation of energy balance, modulate the production of leptin by the adipocyte [52, 53]. It has also been proposed that some of the variability in leptin concentration may be attributable to genetics. However, except for the recent report of congenital leptin deficiency in two obese individuals.
from the same highly consanguineous pedigree [54]. Genetic evidence for a common defect of the human OB gene is lacking [55, 56]. While more studies are needed to establish the molecular mechanisms of OB gene expression, it is clear that at each degree of fatness some individuals can be characterized by “relative” high, normal or low plasma leptin concentrations. Ravussin et al. [57] have recently observed that in Pima Indians low relative plasma leptin concentration is associated with body weight gain (Fig. 3), suggesting that hypoleptinemia may produce or be associated with alterations of energy metabolism favouring obesity. If hypoleptinemia is a characteristic trait of individuals predisposed to obesity, one should also predict that leptin concentration will fall below “normal” when morbidly obese patients are reduced to near-normal body weight. We have recently reported that post-obese women, who lost body weight after a surgical treatment for obesity (biliopancreatic diversion) and maintained a reduced body weight, had low fasting plasma leptin concentration for their body fatness when compared to morbidly obese or normal weight, never-obese women [58], which suggests that hypoleptinemia may also be responsible for body weight relapse after weight loss.

RELATIONSHIPS AMONG RISK FACTORS OF BODY WEIGHT GAIN

We have reviewed the experimental evidence that, in humans, body weight gain is predicted by abnormalities of energy metabolism (low RMR, low spontaneous physical activity and high respiratory quotient), SNS activity and plasma leptin concentration. We shall now examine the experimental evidence for the relationship among these abnormalities (Fig. 4).

SNS activity and metabolic risk factors of body weight gain – The relationship between SNS activity and energy expenditure is well established. Reduction of sympathetic outflow causes a decrease in RMR, and the magnitude of the decrease in RMR is related to the initial value of RMR [59]. Furthermore, noradrenaline turnover and microneurography studies have indicated that the variability in RMR and the variability in SNS activity are strongly related [60, 39]. Thus, taken together, these studies indicate that SNS activity modulates RMR, the largest component of daily energy expenditure, and that a low SNS activity is likely to be associated with a low energy expenditure.

It is also evident that physical activity and exercise increase SNS activity. However, it is not known whether the physiologic variability in SNS activity is related to the level of free-living physical activity. To date, only one study has shown that the noradrenaline appearance rate correlated with spontaneous physical activity measured in resting condition in a respiratory chamber [61]. The results of this study seem to suggest that SNS activity is also a determinant of the level of spontaneous physical activity (or fidgeting), a component of daily energy expenditure that can account for a significant amount of energy.

We have recently shown that SNS activity is negatively correlated with 24-h respiratory quotient, i.e.
daily whole-body carbohydrate-to-lipid oxidation ratio [62], indicating that individuals with a low SNS activity also have a high carbohydrate-to-lipid oxidation ratio. This suggests that SNS activity not only modulates energy expenditure but also plays a role in nutrient partitioning.

**Leptin and metabolic risk factors of body weight gain** – Salbe et al. [63] have recently reported a positive correlation between leptin and energy expenditure and physical activity in 5- to 10-year-old Pima Indian children, suggesting that in humans, as in rodents [44-46], leptin may modulate not only energy intake but also energy expenditure. We and others have also recently shown that a low plasma leptin concentration is associated with a high respiratory quotient [64, 65]. This is in agreement with recent findings of a possible effect of low leptin concentration on body weight, not only via high food intake but also via low fat oxidation [66].

**Leptin and SNS activity** – Administration of recombinant leptin in rodents has been shown to directly stimulate sympathetic nervous system activity, possibly via its inhibitory effect on neuropeptide Y [67, 68]. We have recently reported that a positive correlation exists in humans between muscle sympathetic nerve activity (MSNA) and leptin, which is of the same magnitude as the correlation between MSNA and percent body fat [69]. Although a full understanding of the relationship between leptin and the SNS in humans requires further studies, including administration of leptin, this evidence suggests that in humans, as in animals, leptin may exert a stimulatory effect on SNS activity. Furthermore, because β-adrenergic stimulation decreases leptin expression in vivo [70] and in vitro [71], it is possible that leptin acts centrally by stimulating sympathetic outflow, and sympathetic outflow in turn decreases leptin secretion, thus indicating the existence of a feedback, regulatory loop between adipose tissue and the brain.

**CONCLUSIONS**

The human brain has a paramount importance in the regulation of body weight. The central nervous system monitors the nutritional status of the organism by means of several peripheral afferent signals (including adipocyte-secreted leptin) and reacts to changes in energy stores by modulating the output of its efferent signaling systems (autonomic nervous system and endocrine organs), thus influencing energy intake and energy expenditure. Leptin, produced by the adipocytes in proportion to the degree of adiposity, acts centrally by stimulating sympathetic outflow, which in turn decreases leptin secretion in what seems to be a feedback, regulatory loop. A stable body weight thus results from an equilibrium between input and output signals, and when the equilibrium is disturbed, changes in body weight arise. We and others have shown that hypoleptinemia and a low SNS activity are associated with body weight gain in humans. In our view, hypoleptinaemia (or functional leptin deficiency – i.e. leptin resistance) plays a central role in the pathophysiology of obesity. By insufficient stimulation of the SNS, hypoleptinemia causes alterations of energy metabolism (i.e., low RMR, low spontaneous physical activity, and high respiratory quotient), favouring a positive energy balance and, as a consequence, body weight gain (Fig. 4). Therefore, the adipocyte and the SNS represent likely targets for the treatment of obesity. However, given the large number of neurohormones involved in the signal transduction pathways downstream of leptin and upstream of the autonomic efferences, a quick pharmacological fix for obesity seems, at this point, unlikely. Until we gain more insight into the regulation of food intake, energy expenditure and nutrient partitioning in humans, diet and exercise will remain the only safe and effective treatments against body weight gain.

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