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GENES INVOLVED IN OBESITY: ADIPOCYTES, BRAIN AND MICROFLORA

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ABSTRACT: ***The incidence of obesity and related metabolic disorders such as cardiovascular diseases and type 2 diabetes, are reaching worldwide epidemic proportions. It results from an imbalance between caloric intake and energy expenditure leading to excess energy storage, mostly due to genetic and environmental factors such as diet, food components and/or way of life. It is known since long that this balance is maintained to equilibrium by multiple mechanisms allowing the brain to sense the nutritional status of the body and adapt behavioral and metabolic responses to changes in fuel availability. In this review, we summarize selected aspects of the regulation of energy homeostasis, prevalently highlighting the complex relationships existing between the white adipose tissue, the central nervous system, the endogenous microbiota, and nutrition. We first describe how both the formation and functionality of adipose cells are strongly modulated by the diet before summarizing where and how the central nervous system integrates peripheral signals from the adipose tissue and/or the gastro-intestinal tract. Finally, after a short description of the intestinal commensal flora, ranging from its composition to its importance in immune surveillance, we enlarge the discussion on how nutrition modified this perfectly well-balanced ecosystem.***

KEY WORDS: Adipogenesis, Adipose Tissue, Macrophage, Metabolic Syndrome

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Obesity and obesity-related disorders such as cardiovascular diseases and metabolic abnormalities including hypertension, hyperinsulinemia, insulin-resistance and type 2 diabetes, are among the most pressing problems in the industrialized world (Friedman, 2003; Kannel et al., 1991). Interestingly, the extreme systemic or localized loss of adiposity (*i.e.* lipodystrophy) can also frequently predispose to the same medical conditions (Reitman et al., 2000), demonstrating that normal adipose tissue development and function is critical for metabolic homeostasis.

Obesity results from complex interactions between genes and environmental factors such as diet, food components and/or way of life, and can be viewed as an energy storage disorder in which weight gain results from an energy imbalance (*i.e.* energy input exceeding output), with most of the excess calories stored as triglycerides in adipose tissue (Smith et al., 2006). Therefore a great deal of attention has focused on the mechanisms controlling food intake and adipose mass, and is of considerable importance for public health and clinical medicine.

In this review, we prevalently highlight the complex relationships existing between the white adipose tissue, the central nervous system, the endogenous microbiota, and nutrition. Throughout, we emphasize the most recent findings in the field and consider how it shapes the past knowledge and forecasts the future of research on metabolic disorders, such as obesity.

I. Adipocytes, Genes and Nutrition.

I.1. Adipose tissue: adipocytes and macrophages.

The traditional view of adipose tissue has recently switched from a passive energy "reservoir" with insulatory attributes to a complex, highly active and essential metabolic and endocrine organ, churning out an assortment of hormones and other signals regulating the whole-body physiology (*e.g.* food intake, body weight and brain activity).

Adipose tissue consists of approximately one third of fat cells *i.e.* adipocytes, whereas the remaining 2/3 represent a combination of small blood vessels, connective tissue matrix, nerve tissue and stromal vascular cells; such as pre-adipocytes in various stages of development. All these components of the adipose tissue function as an integrated unit that allows fatty acid accumulation in adipocytes after a meal and fuel distribution to the entire organism between meals.

The formation of adipose cells from mesoderm begins from mid to late gestation. Adipose tissue is rapidly organized after birth as a result of increased size of existing fat cells and proliferation of precursor pre-adipocyte cells. Thereafter, new fat cells can be generated throughout life as a function of environmental factors, especially according to nutritional status (Faust et al., 1978; Faust et al., 1984; Miller et al., 1984; Fève 2005).

Additionally, one key feature of adipose tissue is its endowment in striking plasticity properties exemplified by the dramatic anatomical changes of this tissue under nutritional stimuli. As we will evoke in a following section of this review, the size of the adipose tissue stores increases in period of positive energy balance and decreases when energy expenditure is in excess.

The expansion of adipose tissue mass and cellularity during obesity appears not restricted to the sole increase in number and size of adipocytes. In particular, a progressive infiltration by macrophages is observed in adipose tissue as obesity develops (Weisberg et al., 2003; Xu et al., 2003). These accumulating macrophages are mainly responsible for the up-regulation of inflammatory-related genes observed in obese fat tissues, such as Tumor Necrosis Factor-alpha (TNF-a) or Interleukin-6 (IL-6) (Dandona et al., 1998; Bastard et al., 2000), leading to the suggestion that adipose tissue in obesity is a pro-inflammatory condition, referred to as "obesitis" (Schmidt and Duncan, 2003).

With the "obesity epidemic", the capacity to store energy has earned increasing notoriety for adipose tissue and consequently pushed the adipocyte into the limelight, leading to intensive researches in the cellular and molecular mechanisms underlying adipose tissue development and adipocyte formation. We will now review the main features of adipogenesis, with a special emphasis on gene expression during this dynamic process.

I.2. Adipocyte formation: the process of Adipogenesis.

The number of adipocytes present in an organism is determined to a large degree by the adipocyte differentiation process *i.e*. adipogenesis, which generates mature adipocytes from precursor cells. Basic adipocyte number is established by adolescence in both humans and rodents, although one retains the capacity to generate new adipocytes at all ages. Originally, adipose cells are derived from pluripotent stem cells during a process involving a complex communication network between several transcription factors, some of which being sensors for nutrients.

Most of the molecular details of adipogenesis are now known and have been exhaustively described. This differentiation programme cannot simply be viewed as a hierarchy of molecular events with a modulation in the expression of early, intermediate and late genes (Gregoire et al., 1998; Rangwala and Lazar, 2000; Rosen et al., 2000; Ntambi and Young-Cheul, 2000). Instead, adipogenesis should be regarded as a continuum of overlapping molecular events under the tight control of many factors such as nutrients, finely regulating the sense and the magnitude of the adipose conversion process.

I.2.a: Transcriptional factors controlling adipogenesis.

The mechanisms of adipogenesis were first detailed using cloned pre-adipocyte lines having the potential for differentiation in culture, before being further supported by studies in transgenic mice. It showed that several pro- and anti-adipogenic transcription factors are involved in adipocyte differentiation (recently reviewed by Fève, 2005).

First, adipogenesis is positively regulated by the coordinated expression and activation of several transcription factor families such as the CCAAT/enhancer binding protein (C/EBP), peroxisome proliferator-activated receptor (PPAR) and sterol regulatory element-binding protein-1c (SREBP-1c) families (recently reviewed by Rosen, 2005).

Among members of the PPAR family, the "champion" of adipocyte differentiation is PPAR-γ (Lowell, 1999). Mainly expressed in adipose tissue, PPAR-γ heterodimerizes with retinoid X receptor (RXR) and regulates transcription of target genes through binding to specific peroxisome proliferator response elements. The precise nature of endogenous PPAR-γ ligands is not yet clear, nevertheless various fatty acids, notably originating from nutrients, are able to activate PPAR-γ (Willson et al., 2001; Al-Hasani and Joost, 2005; Sampath and Ntambi, 2005).

The key role of PPAR-γ in adipose conversion is reinforced by the observation that polymorphisms and mutations in **PPARG**, notably those resulting in production of transactivation-defective proteins, are linked to decreased adiposity in humans (Gurnell et al., 2003; Knouff and Auwerx, 2004). Complementary, whereas total lack of PPAR-γ is embryonically lethal in mice (Barak et al., 1999; Kubota et al., 2003), mouse models presenting reduced PPAR-γ activity in adipose tissue display a systemic reduction of fat pad mass (Kubota et al., 2003). Similarly, targeted deletion of PPAR-γ activity in adipose tissue results in progressive loss of both subcutaneous and epididymal fat pads (Zhang et al., 2004). These mouse models, and several others, strongly demonstrate that the levels of PPAR-γ expression in adipose tissue is essential in the determination of total body fat mass.

PPAR-γ is not the sole transcription factor that positively regulates adipocyte differentiation. Members of the C/EBP family (a, b, and d) and SREPB-1c are also significantly elevated during this process, although their expression is not exclusively restricted to adipose tissue. Despite being expressed relatively late during adipogenesis, the crucial role of C/EBP-a is clearly demonstrated in the knockout mouse that presents a major reduction in the lipid content of fat tissue (Wang et al., 1995). Regarding C/EBP-b and -d, their expression occurs very early during adipogenesis and is essential for the proper expression of PPAR-γ. Mice lacking both C/EBP-b and -d exhibit a decrease in adipose tissue development (Tanaka et al., 1997).

Lastly, SREBP-1c both enhances adipose conversion by promoting PPAR-γ expression and activity (Kim et al., 1998; Fajas et al., 1999) and plays an essential role in the regulation of the two major lipid pathways leading to fatty acid storage in mature adipocytes.

Second, in addition to this positive transcriptional control of adipogenesis, some factors have been reported to negatively

regulate this process. To name some but a few, two members of the GATA family of zinc finger transcription factors able to bind to a common (A/T)GATA(A/G) DNA consensus sequence: GATA-2 and GATA-3, exert an inhibitory effect on adipose conversion, likely through decreasing PPAR-γ promoter activity (Tong et al., 2000). Similarly, mice overexpressing the forkhead transcription factor FOXC2 in adipose tissue are lean and more sensitive to insulin (Cederberg et al., 2001).

I.2.b : Environmental factors controlling adipogenesis.

Numerous environmental factors such as hormones, cytokines or nutrients either promote or block the process of adipocyte differentiation.

Exemplifying the promoting factors, glucocorticoids (GCs) have been reported to be potent inducers of adipogenesis, mostly by activating the expression of both C/EBP-d and PPAR-γ (Cao et al., 1991; Wu et al., 1996). Reinforcing this positive role of GCs in adipogenesis is the observation that both human and murine obesities are associated with hypercortisolism (Livingstone et al., 2000; Rask et al., 2001). Insulin is also a crucial factor promoting adipogenesis and fat-specific disruption of the insulin receptor gene induces decreased adiposity in fat-specific insulin receptor knock-out (FIRKO) mice (Blüher et al., 2002). Additionally, the prostaglandin $PG_{12,}$ which is a major metabolite for arachidonate in adipose tissue, also favors adipocyte differentiation by inducing C/EBP-b and -d (Aubert et al., 2000). Interestingly, adipocyte-secreted factors such as adiponectin, can also present pro-adipogenic properties, as recently reported (Fu et al., 2005).

On the opposite, several environmental factors have been described that repress adipogenesis. Growth hormone (GH) stimulates lipolysis, consequently leading to decreased adiposity *in vivo*, and inhibits pre-adipocyte differentiation *in vitro* (Wabitsch et al., 1995). Unlike PG_{12} and adiponectin, two adipose-secreted factors: prostaglandin F2-a and resistin inhibit adipose conversion (Serrero et al., 1992; Kim et al., 2001). Interestingly, despite the fact that elevated levels of circulating cytokines such as TNF-α and IL-6 are associated with increased fat mass and obesity (Dandona et al., 1998; Bastard et al., 2000), those factors have been convincingly reported as being potent inhibitors of adipocyte differentiation (Gimble et al., 1994), notably through suppression of PPAR-γ activity (Suzawa et al., 2003). In line with these observations are the phenotypes of either IL-6 or TNF-α knockout mice, both fatter than controls (Wallenius et al., 2002; Xu et al., 2002).

Considering now the role of nutrients as environmental factors controlling adipogenesis, it has been shown that diet-derived fatty acids can either promote or block adipogenesis, depending on their chain length and their degree of desaturation, but also according to the localisation of the adipose tissues (recently reviewed by Al-Hasani and Joost, 2005; Madsen et al., 2005). To exemplify this, it is known that polyunsaturated fatty acids of the ω-6 series are more adipogenic both *in vitro* and *in vivo*, as compared with their ω-3 counterparts (Massiera et al., 2003), and ω-3-enriched diet was even shown to be protective against obesity by favouring oxidation at the expense of storage (Raclot and Oudart, 1999). Besides acting on adipogenesis *via* their metabolites such as arachidonic acid or prostaglandins, diet-derived fatty acids are also able to directly bind to nuclear receptors like PPAR-γ, and thus have a direct effect on gene expression, adding a supplementary level of complexicity in the control of adiposity by fatty acids.

Beside fat, and among many other nutrients originating from diet that controlled adiposity, retinoic acid (RA), the carboxylic acid form of vitamin A, has emerged as a factor strongly influencing adipocyte differentiation (reviewed by Bonet et al., 2003) either by promoting (low doses) or inhibiting (high doses) *in vitro* adipogenesis. *In vivo*, diets, which are poor in RA, favoured adipose tissue formation, whereas acute RA treatment led to a strong decrease of body fat content (Ribot et al., 2001). Again, these changes of adiposity in response to vitamin A were associated with alterations in PPAR-γ expression.

Obviously, lipogenesis, the development and function of adipose tissue, is responsive to dietary changes and it is the diet itself, *i.e*. carbohydrates, fatty acids and their metabolites, that induces the appropriate cellular programming, *via* the nutrient sensors, to make sure that the nutrients are correctly processed and stored.

I.3. Adipose tissue and calorie restriction.

Intentional weight loss by the mean of calorie restriction (CR) is known to improve most of the medical complications associated with obesity (Case et al., 2002). Indeed, dietary interventions such as fasting or food restriction based on low- or very low-caloric diets, constitute efficient therapeutic approaches to promote fat mass loss in obese patients. Nevertheless, although the beneficial of CR has been shown for many years and appears to come from changes in adipocytes and non-adipose cells from adipose tissue, its precise molecular mechanism remain largely unknown.

In case of prolonged fasting or heavy calorie restriction, some adipocytes shrink and adopt an elongate- or star-shaped phenotype, due to delipidation process (Blanchette-Mackie and Scow, 1981). Recently, numerous studies have exploited the micro-array approach (Leung and Cavalieri, 2003) to monitor changes in adipose tissue gene expression during calorie restriction.

In mice, compared with non-fasted controls, either 1 day-fasting or short CR (*i.e*. 23 days) has a slight effect on gene expression, contrasting with long CR (*i.e*. 9 months) which notably up-regulates the expression of SREBP-1c (Higami and Pugh, 2004). In addition, the effects of CR on fat mass loss have been studied in the genetic model of obesity resulting from leptin-deficiency (*ob*/*ob* mice, (Zhang et al., 1994)) and compared with the ones induced by leptin administration (Halaas et al., 1995). This study identified 8 groups of genes whose expression was different between leptin treatment and CR, suggesting that the energy restriction by itself may regulate adipose tissue gene expression independently of the fat mass loss (Soukas et al., 2000).

Therefore, during adaptation to CR, fat is mobilized from WAT and adipocytes remain with minimal fat stores. It was recently proposed that sirtuins, acting through down-regulation of PPAR-γ,

play a dominant role in these changes in WAT in response to CR, thus representing a molecular link connecting caloric restriction to reduced fat accretion (Guarente, 2005).

Considering the resulting effects of calorie restriction in humans, it was recently reported that CR affects genes involved in metabolism and improves the inflammatory profiles (Viguerie et al., 2005), therefore unravelling new aspects of adipose tissue biology such as the relationship between obesity and inflammation (Greenberg and Obin, 2006). Further experiments are required to investigate the nature of the regulation of inflammatory markers during nutritional challenge and to determine if the modifications observed during calorie restriction result from phenotypical changes of resident macrophages and/or to a new monocyte/macrophage infiltration in the adipose tissue.

I.4. Adipose tissue and obesity : the diet-induced obesity (DIO) model.

As previously stated, excess of adipose tissue mass *i.e*. obesity, arises from increased size of individual adipose cells due to lipid accumulation and/or from increased number of adipocytes arising from differentiation of adipose precursor cells to mature adipocytes under the appropriate nutritional and hormonal cues.

A large number of genetically-manipulated animal models, mostly mice, have been created for the study of adipose tissue biology. These models have been extensively and frequently reviewed (Blüher, 2005). Nevertheless, despite having permitted to add key pieces to the complex puzzle of adipose tissue physiology, transgenic animal models have limitations and may not always necessarily match the human disease. In this regard, the diet-induced obesity (DIO) model may better reproduce human obesity than the genetic models. Recently, Moraes *et al*. (2003) reported, using oligonucleotide micro-array analysis, that approximately 500 genes were differentially expressed in adipose tissue of DIO-C57BL/6J mice. Interestingly, genes coding markers for adipocyte differentiation are down-regulated whereas there is no variation in the expression of the main adipogenic transcription factors, contrasting with the results obtained with adipose tissue from leptin-deficient obese *ob*/*ob* mice (Nadler et al., 2000). This latter observation shows that the gene expression profile in adipose tissue of genetic models of obesity, such as the *ob*/*ob* mice, does not reflect the profile obtained with obesity induced by overfeeding, reinforcing the interest of these rodent models of diet-induced obesity.

In human obesity, recent studies have been conducted on obese adipose tissue using micro-array technology. From those reports, a tendency of down-regulation of genes involved in lipolysis has been described in adipose tissue harvested from obese individuals (Gomez-Ambrosi et al., 2004). Complementary, both the expression of pro-adipogenic transcription factors and adipocyte-specific markers are reduced in the adipose tissue of non-diabetic, insulin-resistant patients, indicating that insulin-resistance may be associated with impaired adipogenesis (Yang et al., 2004). Finally, this technological approach was recently applied to analyse the effect of leptin treatment of obese individuals on the gene expression pattern in WAT (Taleb et al., 2006). Surprisingly, it revealed that leptin treatment mainly impacted on the expression of genes related to inflammation and immunity.

II. Central nervous system, Genes and Nutrition.

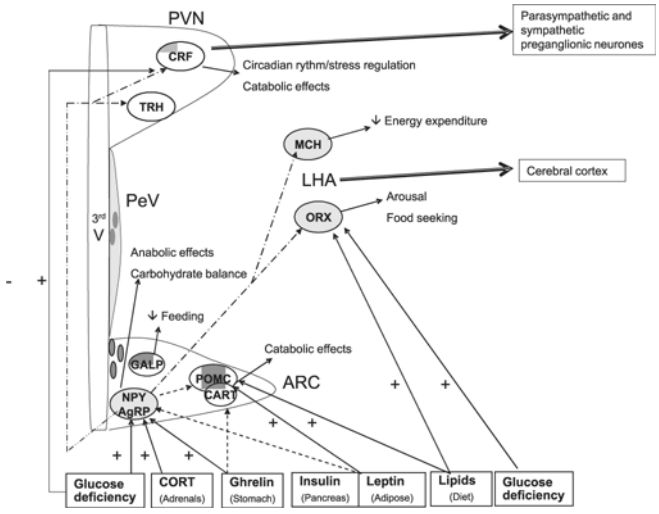
Daily energy intake is variable both among and within individuals, depending on emotional, social or time variables, and is not necessarily correlated with daily energy expenditure (Edholm, 1997). Reducing a behaviour as complex as feeding to a series of molecular interactions may be simplistic, but the recent discoveries over the past few years using genetically-modified murine models enlighten the role of molecules that modulate food intake and participate to energy homeostasis.

II.1. Adiposity signals acting on neurons: an emerging concept for the modulation of food intake?

Growing evidences support the existence of a bidirectional communication between adipocytes and brain. It was first related by Kennedy (1953) who proposed that signals generated in proportion to body fat stores, exert an inhibitory effect in the brain to reduce the food intake.

Besides the pancreatic hormone, insulin, one of the first peripheral signals entering into the brain from the circulation (Baura et al., 1993) to lower energy intake (Woods et al., 1979), other molecules from the gastro-intestinal tract and from adipocytes are implicated in the central control of body weight. Two hormones from the gastro-intestinal tract: ghrelin and cholecystokinin (CCK), are transmitted to the brain *via* vagal afferent, eliciting respectively starvation and satiety signals (Date et al., 2005). Additionally the adipose tissue secretes a cytokine-like molecule encoded by the *ob* gene, the hormone leptin (Zhang et al., 1994) that shares common features with insulin in the central regulation of food intake. Indeed, both hormones are secreted proportionally to body fat content and target the hypothalamus (**Figure 1**). By acting on hypothalamic neurones, insulin and leptin repress the expression of genes involved in anabolic neural circuits that stimulate eating and activate catabolic genes that inhibit food intake and increase energy expenditure (Loktionov, 2003).

FIGURE 1. Schematic drawing adapted from Leibowitz and Wortley (2004, *Peptides*. 25, 473-504) illustrating the neuronal organisation involved in the regulation of food intake and energy expenditure.



II.1.a : Where does the "food intake" message reach the brain?

The need to eat is under complex regulation involving various body compartments such as gastro-intestinal tract, adipose tissue and brain. In the brain, the hypothalamus states as the main central structure that regulates food homeostasis. Two major hypothalamic nuclei "centres" were initially presumed to mediate hunger and satiety : the lateral and the ventromedial hypothalamus. Indeed, lesion of lateral hypothalamus provokes hypophagia (Anand and Brobeck, 1951; Mitchel and Keesey, 1977) whereas hyperphagia is induced by ventromedial hypothalamic lesion (Hetherington and Ranson, 1940; Keesey et al., 1979). Current literature in the field sustains the existence of an even more complex and distributed network, with metabolic signals arising from periphery being processed by sensor neurones organised as anatomically discrete clusters within hypothalamus, amygdala, area postrema and nucleus tractus solitarius (NTS) or by groups of medullary serotonin and catecholamine neurones (Levin, 2001; Levin, 2002). All these neurones display altered membrane potential, firing rate and transcriptional activity when activated by metabolic signals like glucose, fatty acid, lactate, ketone bodies, insulin and leptin (Levin, 2001; Levin, 2002).

Recent molecular, physiological and anatomical studies have provided new insight on the role of the lateral hypothalamic area (LHA) and the mediobasal hypothalamus in the regulation of food intake and body weight. The LHA contains neurons that send fibres throughout the neuraxis including monosynaptic projections to the cerebral cortex (Saper, 1985). Such innervation might play a key role in the integration of the complex physiology underlying the feeding behaviour and the initiation of feeding. Recently, Petrovich *et al.* (2005) have identified forebrain projection neurones to the LHA that are selectively activated by a learned cue that stimulates eating. In this behavioural situation, amygdala and prefrontal cortex neurones express two immediate-early genes having different temporal expression patterns (*Arc*, expressed 2-10 min after neuronal activation and *Homer1a*, which peaks at 25-35 min). These data underline the existence of a direct functional pathway from amygdala and prefrontal cortex to LHA that could play a pivotal role in regulating the impulse to eat in response to appetitive signals with high incentive value.

Moreover, LHA as well as the ventromedial nucleus are targets of inputs coming from arcuate nucleus. Indeed, specific hypothalamic lesions induced by administration of monosodium glutamate (Olney, 1969) or gold thioglucose (Debons et al., 1977), respectively damaging the arcuate nucleus and the ventromedial nucleus, cause obesity and hyperphagia. The arcuate nucleus lies in the ventral hypothalamus, along the third ventricle. It resides above the median eminence and shares connections with the subfornical organ, *i.e.* regions where the blood-brain barrier is compromised (Lind, 1987). Thus, the arcuate nucleus constitutes a key site for integration of peripheral signals in relation with the regulation of feeding, as its neurons express leptin receptors (Elmquist et al., 1998). Indeed, viral transfection of leptin receptor in arcuate neurons is sufficient to cause reduction of food intake in leptin-receptor deficient mice (Morton et al., 2003). Moreover, Zucker fatty (*fa/fa*) rats, deficient in functional leptin receptors, develop hyperphagia on postnatal day 12 (Kowalski et al., 1998; Kowalski et al., 1999). Taking in consideration these data, Bouret *et al.* (2004a, 2004b) recently demonstrate the trophic role of leptin in the formation of projection pathways from the arcuate nucleus to dorsomedial hypothalamic nucleus, hypothalamic paraventricular nucleus (PVN) and LHA in neonatal mice from postnatal days 5 to 16. In particular, exogenous leptin treatment of leptin-deficient *ob/ob* neonate mice rescues the development of arcuate nucleus projections (Bouret et al., 2004a). Thus, the hypothalamic projections of arcuate nucleus point out its participation to monitor the leptin-signalling throughout the brain.

II.1.b : How do brain genes "integrate the food signals"?

Signals coming from the periphery are integrated by metabolic sensor neurons and their summated activity is transmitted *via* neural and hormonal outputs to the periphery. Energy homeostasis is centrally controlled by transmitters such as gamma-aminobutyric acid (GABA), glutamate, catecholamine or serotonin and neuropeptides both found in various parts of the brain, but also in peripheral organs such as the gut (Berthoud, 2002). Among the variety of hypothalamic factors that mediate energy homeostasis, some exert an orexigenic action whereas others are anorexigenic (**Table 1**).

TABLE 1. Description of the main hypothalamic neuropeptides involved in the regulation of food intake and energy expenditure.

OREXIGENIC MOLECULES	LOCATION	REGULATION (↑↓) BY FOOD INTAKE SIGNALS	
NPY	ARC	↓ leptin/insulin	↑ ghrelin
AgRP	ARC	↓ leptin/insulin	↑ ghrelin
MCH	LHA	↓ leptin/insulin	
Hypocretin 1 & 2	LHA	↓ leptin/insulin/glucose	↑ ghrelin
Ghrelin	ARC, PeV		
ANOREXIGENIC MOLECULES			
POMC	ARC	↓ ghrelin	↑ leptin/insulin
CART	ARC		↑ leptin/insulin/adiponectin
CRH	PVN		↑ leptin/insulin/IL-1β
TRH	PVN		↑ leptin/insulin

The central mechanisms regulating feeding usually require a variety of neurotransmitters that exert more a modulatory effect than an executive one. These neuromediators are clustered in various parts of the brain and their widespread innervations target different cerebral structures involved directly or not in food intake. As an example, the meso-limbic dopaminergic system contributes to give a hedonic/rewarding value of the food. This component is under the regulation of GABAergic and/or glutamatergic neurones. Furthermore, the brain serotonin (5-HT) systems also contribute to regulate eating behaviour and energy homeostasis as mice exhibiting a mutated 5-HT_{2C} receptor gene show hyperphagia independent from leptin plasma levels (Tecott et al., 1995; Nonogaki et al., 1998). Additionally, the 5-HT_{1B} receptors mediate the anorexic actions of the 5-HT (Lee et al., 2004). In 24h-fasted mice, the hypothalamic 5-HT_{1B} receptor and 5-HT_{2C} receptor mRNA levels are augmented in parallel with the increase of plasma active ghrelin levels (Nonogaki et al., 2006).

As previously evoked, LHA and arcuate nucleus constitute key hypothalamic structures to integrate food signals. The LHA is composed by neuronal populations containing melanin-concentrating hormone (MCH), that is also present in neurones of the hypothalamic perifornical area and zona incerta (Bittencourt et al., 1992), and orexin (ORX, (Sakurai et al., 1998)) also called hypocretins (HO, (De Lecea et al., 1998)). These latter peptides, when intracerebroventricularly injected, increase food intake; their mRNA are also elevated during fasting (Sakurai et al., 1998; Qu et al., 1996). The MCH and ORX neurones receive inputs from the neuropeptide Y- (NPY), Agouti-related protein- (AgRP) and a melanocortin stimulating hormone- (α-MSH) immunoreactive fibres coming from the arcuate nucleus (Elias et al., 1998). Such innervation may link peripheral metabolic signals to cerebral cortical areas in order to generate the feeding sensation.

Regarding the arcuate nucleus, it contains populations of neurons that play an important role in distributing leptin signals in the brain. A first neuronal population contains the orexigenic neuropeptide NPY. Most of these neurons project to the PVN (Bai et al., 1985). In fact, intra-PVN injection of NPY increases food intake, more specifically carbohydrate intake (Stanley et al., 1985). Arcuate NPY neurons also send innervation to amygdala, an area also involved in feeding behaviour since lesion of amygdala produces obesity and increases preference for high carbohydrate diet (King et al., 1998; King et al., 2003). When administrated into the amygdala, NPY selectively reduces high fat food intake and preference, without altering total caloric intake (Primeaux et al., 2006). As an antisense inhibition of NPY-Y1 receptor expression blocks the anxiolytic-like action of NPY in amygdala and increases feeding, amygdalar effects of NPY may be related to the overall emotional state: a NPY-induced reduction in anxiety might be responsible for the NPY-induced reduction in fat intake. A high percentage of NPY neurons co-express AgRP (Hahn et al., 1998). The agouti mutation (A^g/a) includes an over-eating/obesity syndrome distinct from that seen in the *ob/ob* mice, as it is due to antagonism of type 3 and 4 of the melanocortin receptors (Fan et al., 1997). During fasting, the AgRP mRNA is increased, suggesting its orexigenic properties. Besides NPY/AgRP neurons, arcuate nucleus also contains another subpopulation of neurons containing melanocortin peptides (⟨–MSH), the proopiomelanocortin (POMC) gene product, and characterized by their anorexigenic effects. In the *ob/ob* mice or in fasted rodents, the markedly reduced POMC mRNA expression can be prevented by exogenous leptin administration (Schwartz et al., 1997; Thornton et al., 1997). POMC neurons innervate the PVN, the melanocortin concentrating hormone (MCH) and ORX/HO neurons of the LHA, as well as sympathetic preganglionic neurons (Saper et al., 2002). Finally, another peptide is expressed in the arcuate nucleus: CART (cocaine and amphetamine related transcript) (Couceyro et al., 1997; Koylu et al., 1997). The CART-neurons modulate feeding behaviour since central injection of a CART-specific immunserum, increases food intake (Koylu et al., 1997). Moreover, as previously stated for POMC neurons (Schwartz et al., 1997; Thornton et al., 1997), administration of leptin provokes an elevation of CART mRNA (Kristensen et al., 1998). Virtually all arcuate CART neurons coexpress POMC (Elmquist et al., 1999). The sites of action of these leptin-regulated CART neurons that may be involved in the inhibition of food intake are currently unknown even if some evidences show the presence of terminals on central autonomic sites, like the sympathetic preganglionic spinal cord neurons (Koylu et al., 1997). Altogether, these hypothalamic neurons constitute a complex network ensuring connections to acutely regulate peripheral signals and to spread them within the brain.

II.1.c : Hypothalamic integration of the leptin signal.

As underlined before, leptin action illuminates the hypothalamic satiety network. Its existence was hypothesized by Coleman *et al.* (1969; 1973) in studying two mutant mouse strains, namely the *ob/ob* and *db/db* mice which have a phenotype of massive overeating, obesity and delay of sexual maturation. Further, this peptide hormone was cloned and demonstrated to be mainly synthesized by adipose cells (Zhang et al., 1994), in proportion to the adipose-cell mass (Maffei et al., 1995) although a recent study reports a partial leptin-deficiency in patients having an increased body fat mass (Farooqi et al., 2001). Leptin release occurs in response to a food intake signal to act both peripherally and in the brain (Auwerx and Staels, 1998). Leptin enters the brain *via* transporters across the blood-brain barrier and reaches the hypothalamic targets described above. This transport is decreased in diet-induced obesity (DIO) and aging, and might contribute to leptin resistance, excess adiposity and glucose intolerance (Banks et al., 1999). It was shown that systemic injection of leptin induces expression of the immediate-early gene *c-fos* in arcuate nucleus, ventromedial nucleus, dorsomedial nucleus, and ventral parvocellular part of the PVN (Elmquist et al., 1997).

Leptin receptors are members of the cytokine-receptor superfamily (Tartaglia et al., 1995; Tartaglia, 1997). Especially, leptin binds to cytokine type I receptors, which signal through the JAK (janus kinases) - STAT (signal transducer and activator of transcription) pathway (for more details see (Tartaglia et al., 1995; Schwartz et al., 2000)).

Interestingly, in the central nervous system, leptin receptors are expressed in the hypothalamus (arcuate, dorsomedial, ventromedial nuclei, PVN and LHA), but also in several brainstem areas, like nucleus tractus solitarius (NTS)(Ahima, 2005). Leptin receptors are present on arcuate NPY/AgrP neurons (Elmquist et al., 1998), mediating the effects of leptin on food intake. An increase of leptin or high-fat diet suppresses these peptides, particularly by an activation of inhibitory components of the JAK-STAT pathway, the suppressor of cytokine signalling 3 (SOCS-3) (Bjorbaeck et al., 1998). SOCS proteins are rapidly induced by activation of the type I cytokine family receptors, among which leptin and IL-6 receptors (Tartaglia et al., 1995). Moreover, leptin increases levels of the arcuate anorectic peptides, αMSH and CART, as leptin receptor mRNA is coexpressed in a very high percentage of arcuate POMC neurons (Cheung et al., 1997; Ahima, 2005).

Recently, leptin has been demonstrated to act also directly on ventromedial hypothalamus where it depolarizes and increases the firing rate of steroidogenic factor-1-positive neurons (Dhillon et al., 2006). The steroidogenic factor-1, is a transcription factor expressed in the ventromedial hypothalamus, essential for the normal development of this hypothalamic structure. Indeed, steroidogenic factor-1 gene KO mice have abnormal ventromedial hypothalamus development and are obese (Majdic et al., 2002). Furthermore, transgenic mice that lack leptin receptors on these steroidogenic factor-1-positive neurons increase food consumption and fat stores (Dhillon et al., 2006).

In human, impressive is the finding that treatment with leptin reverses the obese phenotype in leptin-deficient humans (Farooqi et al., 2002). In contrast, the majority of obese patients have high circulating leptin levels (Caro et al., 1996), strongly suggesting the existence of leptin resistance in hyperleptinemic obese subjects. The cause of leptin resistance in most forms of human and rodent obesity is not yet fully defined. Nevertheless, as we stated above, in DIO mice, a classical mouse model of leptin resistance and obesity, it was shown that the level of suppressor of cytokine signaling 3 (SOCS-3), an inhibitor of leptin signaling, is increased in the arcuate nucleus of DIO mice, bringing a clue to the molecular mechanisms underlying the development of central leptin resistance (Münzberg et al., 2004). The central action of leptin described above, adds to the one of other peripheral factors, notably those originating from the intestinal tract.

II.2. The appetite/satiety signals: from periphery to neurons.

The short-term regulation of food intake at central level involves various peripheral factors including gastric mechanoreceptors, metabolic substrate signals, gastro-intestinal hormones, and other peripheral hormones (Figure 2).

II.2.a : Signals from gastro-intestinal mechanoreceptors.

Gastro-intestinal mechanoreceptors sensitive to volume detection intervene directly *via* the vagus nerve in the short-term satiety. Precisely, the two putative mechanoreceptors that the vagus nerve supplies to gastrointestinal smooth muscle are intraganglionic laminar endings (IGLEs) and intramuscular arrays. A knock-out mice model, deficient in the neurotrophin-4 (NT-4) gene, exhibits selective losses of these endings. As a consequence, these mutants show a substantial organ-specific reduction of IGLEs, mostly in the small intestine. These morphologic changes are linked with a differential meal pattern characterized by increased meal durations with solid food and increased meal sizes with liquid food without any modifications in the daily total food intake and body weight. Thus, this work ascertains that NT-4 may participate in short-term satiety, probably by conveying feedback about intestinal distension or transit to the brain (Fox et al., 2001).

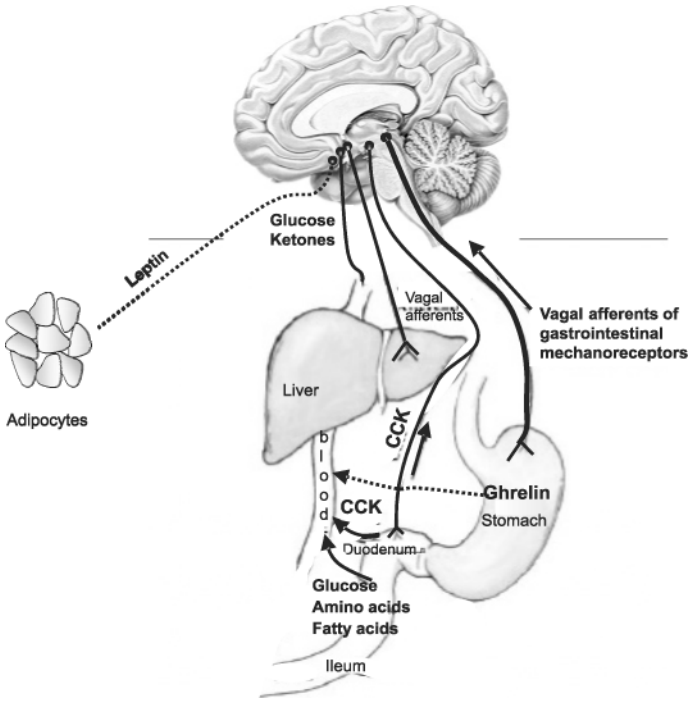
II.2.b : Signals from nutrients.

Changes in the circulating levels of nutrients such as ketone, fatty acids and/or glucose contribute to modulate food intake in animals (Smith and Epstein, 1969, recently reviewed in Prodi and Obici, 2006) as well as hunger sensations and food intake in humans (Thompson and Campbell, 1977).

Ketones, products of the hepatic fatty acid oxidation, are released into the central and peripheral circulation and provide a feedback signal for control of feeding since inhibitors of fatty acid oxidation generate a hyperphagic state (for review see Scharrer, 1999). In humans, Kamphuis et al. demonstrate that diacylgycerol treatment increases fat oxidation and appetite (Kamphuis et al., 2003). The feelings of hunger, appetite, estimated prospective food intake, and desire to eat augment significantly after two days with diacylgycerol treatment without altering energy expenditure. The exact location of metabolic neuronal sensors responding to fatty acid oxidation and controlling food intake still remains largely unknown. However, the feeding responses of rats to fat depends on intact abdominal vagal afferents that project to brainstem structures, the NTS and the adjacent circumventricular area postrema, important relay for visceral and gustatory afferents. Recently, Laugerette et al. (2006) brought a molecular explanation for the fatty-food preference, that is localized in the oral cavity. Indeed, increased palatability of foods could partly override the feeling of satiety and result in hyperphagia. Among foods, dietary fats are certainly the more palatable and, in addition to their high caloric nature, directly influence food intake (Warwick et al., 2003). The authors reported the participation of CD36 (a fatty acid transporter and scavenger receptor for oxidized Low Density Lipoprotein), as a taste receptor for fatty acids in lingual papillae, leading to spontaneous fat preference and digestive secretions. In this study, CD36-null mice showed a lost of palatability of the fat-enriched solutions that was noticed in the wild-type (WT) control animals. Moreover, this effect appeared to be restricted to lipid detection, since the preference for sucrose and the aversion for quinine remained unchanged in CD36-null and WT mice. Nonetheless, CD36 expression seemed to be up-regulated either in *in vitro* culture-derived human monocytes/macrophages, by glucose (Griffin et al., 2001; Hayek et al., 2005) or in different organs and tissues from diabetic animals (small intestine, heart and adipose tissue) (Ibrahimi and Abumrad, 2002; Chen et al., 2006), possibly questioning on the consequence of hyperglycemia on the expression of CD36 in the oral cavity, and thus on the preference for fat.

The general postulate that food intake is affected by plasma glucose levels through the mediation of specialized glucoreceptors

FIGURE 2. Schematic illustration adapted from Havel (2001, *Experimental and Biological Medicine*. 226, 963-977) of the main nutrition signals reaching the brain.



which are sensitive to the fluctuations of blood glucose is an old one, referred to as the "Glucostatic hypothesis" (Mayer et al., 1953). It is known that decreased glucose plasma levels stimulate appetite by influencing the firing rate of specialized neuronal populations in the ventromedial and lateral hypothalamus as their responses increase following application of glucose (Oomura et al., 1969, Levin, 2002).

Finally, several lines of evidence support the notion that lipid metabolism in neurons plays a critical role in mediating hypothalamic responses to fuel availability. Two metabolites, malonyl-conenzyme fatty acyl-CoA (malonyl-CoA) and long-chain fatty acyl-CoAs have emerged as probable signaling molecules in the hypothalamus. The role for malonyl-CoA in regulating food intake was first recognized through the discovery that intraperitoneal or intracerebral administration of inhibitors of fatty acid synthase (FAS), such as cerulenin and C75, causes an accumulation of malonyl-CoA in the hypothalamus and has a profound anorexigenic effect (Loftus et al., 2000). Likewise, intracerebral administration of long-chain fatty acids, e.g. oleic acid, reduces food intake, demonstrating that certain fatty acids do have an inhibitory central effect on feeding control (Morgan et al., 2004). Thus, it appears that under physiological conditions hypothalamic malonyl-CoA is an important determinant of feeding behavior (recently reviewed in Prodi and Obici, 2006).

II.2.c : Signals from gastro-intestinal hormones.

The food intake is strictly controlled by various gastro-intestinal hormones. Each, except the stomach-derived product ghrelin, inhibits food intake. The cholecystokinin (CCK), released from endocrine cells in the mucosal layer of the proximal small intestine following ingestion of dietary fat and small proteins, transmits food signals to hindbrain *via* vagal afferent inputs, by activating CCK_A receptors located in pylorus and liver. In rats, ingestion of a satiating meal or exogenous injection of CCK causes the immediate early-gene *c-fos* expression in the medial NTS (Monnikes et al., 1997; Rinaman et al., 1998; Zittel et al., 1999). Since CCK does not readily cross the blood brain barrier, it acts indirectly on CCK_A receptors located on vagal afferents which terminate in the NTS (Moran et al., 1997) or area postrema (Carlberg et al., 1992), circumventricular organ strongly activated by CCK (Rinaman et al., 1993) and establishing monosynaptic connections with the NTS. A large majority of the CCK-activated NTS neurons are catecholaminergic (Myers and Rinaman, 2002) and send projections to the central amygdala (Myers and Rinaman, 2002), a telencephalic brain area that participates in the regulation of visceral functions, like for example gastrointestinal activities (Jia et al., 1997) in relation with emotional reactivity by its connectivity with hypothalamus (Davis, 2000).

Besides CCK, ghrelin is a hormone synthesized in the stomach which plasma levels increase during food deprivation in animals (Kojima et al., 1999). Originally identified to exert a stimulatory effect on growth hormone secretion *via* a growth hormone secretagogue receptor (Bowers, 2001; Kojima et al., 2001), ghrelin stimulates food intake in satiated rodents (Tschop et al., 2000). Additionally, ghrelin may be involved in meal initiation as a noticeable preprandial increase in its plasma levels has been reported in humans (Cummings et al., 2001). The orexigenic effect of ghrelin appears to be mediated *via* the NPY/AgRP pathway. Indeed, ghrelin administration induces immediate-early gene expression in NPY neurons (Dickson and Luckman, 1997) and provokes increases in the NPY and AgRP mRNA expression in the hypothalamic arcuate nucleus (Kamegai et al., 2000; Asakawa et al., 2001; Nakazato et al., 2001; Shintani et al., 2001) of fed rats as these neurons express ghrelin receptors (Willesen et al., 1999). In humans, the gastric bypass operation of morbidly obese patients results in a marked body weight loss associated with a great reduced ghrelin levels (Cummings et al., 2002). These observations reflect a key role of the ghrelin in the motivation for feeding although the central circuits through which ghrelin exerts its effects remain largely unknown.

Interestingly, one of the "adiposity signal", namely the adipocyte-derived hormone leptin, was recently reported to be secreted by cells of the gastric mucosa and therefore participate to the regulation of meals, leading to viewing gastric leptin as a neuroendocrine key for satiety (Cammisotto et al., 2005). Indeed, leptin is found in the stomach where it is mainly secreted by the lumen (Bado et al., 1998), and leptin receptors have been identified on the intestinal brush borders (Sobhani et al., 2000). Leptin secretion in the stomach is regulated by feeding, with its secretion being rapidly increased following a meal (Attoub et al.,

1999), and intestinal hormones CCK (Bado et al., 1998). Additionally, there appears to be an interaction between CCK and leptin, since leptin can induce CCK release (Guilmeau et al., 2003) and *vice versa* (Bado et al., 1998), leading to a synergistic effect on short-term inhibition of food-intake (Barrachina et al., 1997) and long-term reduction of body weight (Matson and Ritter, 1999).

II.2.d : Signals from peripheral endocrine factors.

Other endocrine factors, like glucocorticoids, thyroid hormones and cytokines, intervene in the brain to regulate food intake. Besides their catabolic effects in the periphery, glucocorticoids exert anabolic effects at the central level, increasing food intake (Tempel et al., 1992). These adrenal hormones exert their orexigenic effects through the hypothalamic neuropeptide systems involved in the inhibition of food intake following release of insulin and/or leptin (Strack et al., 1995; La Fleur, 2006). As an example, using a model of transgenic mice in which the POMC transgene is introduced in mice with a POMC null mutation, in order to re-establish the peripheral melanocortin and corticosterone secretion, Smart *et al.* (2006) demonstrate that restoration of pituitary POMC expression to create a *de facto* neuronal POMC deficiency, exacerbated the development of obesity, largely *via* glucocorticoid modulation of appetite, metabolism, and energy partitioning.

Other steroid hormones such as the thyroid hormones, influence the feeding behavior even if the mechanism of action is again not well understood. In the Graves' autoimmune disease (Graves' thyrotoxicosis), the thyroid gland produce large amount of thyroid hormone, causing lost of weight, despite increased appetite and food intake, therefore suggesting a disturbed balance between energy intake and expenditure. Rojdmark *et al.* (2005) recently show that hormonal factors, known to affect hunger/satiety, change significantly over time as pharmacological treatment turns hyperthyroidism into euthyroidism. Indeed, free T3, T4, and glucose levels drastically decline from hyperthyroidism situation to the restored euthyroidism whereas cortisol, insulin, growth hormone (GH), and leptin levels are similar. Both ghrelin secretion and IGF-1 bioavailability are low in patients with untreated thyrotoxicosis, but increase markedly as pharmacotherapy makes them euthyroid. These data support the works of Lin *et al.* (1983) where central administration of thyrotropin-releasing hormone suppress food intake by exerting a hypothalamic feedback inhibition.

Finally, a number of pro-inflammatory cytokines, like interleukin-6 (IL-6), inhibits food intake (for review see (Plata-Salaman, 1995)). IL-6, mainly produced by macrophages, T lymphocytes and adipocytes, exerts its inhibitory feedback on the body fat mass *via* hypothalamic receptors, and IL-6-deficient mice develop mature onset obesity and decreased glucose tolerance (Wallenius et al., 2002). However, a direct role of this cytokine in food intake regulation under physiological conditions is still not completely established.

II.3. How does the brain modulate the "food intake" ?

The existence of a feedback loop between brain and adipose tissue was recently demonstrated as mature adipocytes express mRNA for the anterior pituitary ACTH, TSH (thyroid stimulating hormone), GH and prolactin receptors while such expression is low in preadipocytes (Schaffler et al., 2005). Most of these hormones have a short half-live, are released rapidly and followed a circadian rhythm (Cohen et al., 1986). Thus, they may regulate the adipocyte function very quickly by modulating adipokine gene expression. The fast-acting adipocyte response to pituitary gland hormones and hypothalamic peptides would potentially give a physiological substrate for a rapid regulation of insulin/leptin sensitivity, lipid synthesis or breakdown, glyconeogenesis, satiety or appetite. Alterations in the gene expression of these receptors might be at the origin of some forms of obesity. As examples, the obesity generally observed in hypothyreosis, which is accompanied by drastic elevation of TSH plasma levels, might be the result on a direct action of TSH on adipocytes to regulate energy metabolism. Additionally, in the Cushing's disease, the excess of fat is commonly explained by the increased cortisol secretion, but could also be due to the related release of ACTH acting on adipocytes.

Taken as a whole, these data reflect the reciprocal dialog between brain, adipocyte and gastro-intestinal tract. A better understanding of how the genes involved in food consumption are regulated remains an essential question. It should ultimately help individuals to better adapt their food intake and thus solve, at least in part, health problems linked to obesity or anorexia and their metabolic/psychological consequences.

III. Endogenous microflora, Genes and Nutrition.

In addition to the central nervous system, the "Enteric Nervous System" is located in sheaths of tissue lining the oesophagus, stomach, small intestine and colon, and holds about 100-million nerve cells more than in spinal cord. Less complex and smaller than the cranial brain, the gut's brain contains between 70 to 85 per cent of the body's immune cells, is an independent data-processing centre handling a complicated circuitry of neurons, neuromodulators and neurotransmitters. As evoked above, the enteric nervous system is in constant interaction with both the adipose tissue and the central nervous system.

In addition to this, the gut also contains an immense number of microorganisms, collectively defined as the microbiota. We will now focused on the impact of intestinal microbiota in normal bowel function and in the maintenance of host's health through metabolic and immunological activities.

III.1. Nutrition and commensal flora.

III.1.a : The commensal flora : definition and importance in immunity.

Human and other mammals are colonized by a vast, complex, and dynamic bacterial community. In human, the number of microbes associated with mucosal surfaces exceeds by 10 times the total number of cells. Constituted of more than 1000 species, the microbial collective genomes are estimated to contain 100 times more genes than the human genome (Savage, 1977). Indeed, recent work using a large-scale comparative analysis of 16S rDNA

sequences of adherent mucosal and fecal microflora, has shown 13,355 prokaryotic ribosomal RNA gene sequences (Eckburg et al., 2005). A large fraction of the dominant gut microbes remains unculturable, 80% of the phylotypes deriving from microorganisms have no culturable representative. The proportion of such un-recognized species increases from birth to the old age. Metagenomics approaches have been initiated to address the collective genomes of the intestinal microbiota, know as the microbiome (Egert, 2006; Zoetendal, 2006). Complementary to metagenomics, meta-transcriptomics, meta-proteomics and meta-metabolomics approaches have been initiated and are expected to provide further insights into the *in situ* activity of the intestinal flora.

In the intestine, microflora is in permanent contact and reciprocal interaction with host cells and nutrients, therefore composing an extremely complex and highly regulated ecosystem. The intestinal microbiota plays an important role in normal gut function and maintenance of host's health. It established immediately after birth and is now considered to be essential in priming the immune system during ontogeny. Different factors contribute to the protective function of gut microflora such as : [1]maintaining a physical barrier against colonization or invasion by pathogens, [2]facilitating nutrient digestion and assimilation, and [3]providing immunological surveillance signals at the gut mucosa-lumen interface. Comparison of conventionally-raised rodents with germ-free counterparts has revealed a series of anatomical, biochemical and physiological phenotypes collectively known as Microflora-Associated Characteristics (MACS) (Hooper et al., 2002).

In addition, the presence of a microflora increases intestinal epithelial turnover. Commensal bacteria may directly influence the intestinal epithelium to limit immune activation. Recently Neish et al. (2000) demonstrated that avirulent Salmonella abrogates production of inflammatory cascade by inhibiting ubiquitination and degradation of IkB, thus blocking the transactivation of NFkB-mediated genes. More recently, Kelly et al. (2004) identified an interesting mechanism by which commensal flora may regulate host inflammatory responses and maintain immune homeostasis, by promoting nuclear export of NFkB subunit relA, through a PPAR-γ-dependent pathway. Similarly, Rakoff-Nahoum et al. (2004) demonstrated that recognition of commensal microflora by Toll-like receptors is required for intestinal homeostasis, explaining why disequilibrium in this signalling pathway can lead to the initiation of inflammatory bowel diseases.

Finally, it has been reported that microflora deconjugates and dehydroxylates bile acids (Moser et al., 2001; Jones, 2004), metabolizes bilirubin (Saxerholt and Midtvedt, 1986), reduces cholesterol (Roller, 2004; Chiu, 2005), and degrades mucus glycoproteins produced by the intestinal epithelium's goblet cell lineage (Hooper et al., 2002).

III.1.b : Microflora composition is influenced by nutrition.

As evoked above, assembly of the gut microflora commences at birth and its composition will undergo dramatic changes during postnatal development. When space and nutrients are not limiting, commensals with high division rates predominate. As the population increases and nutrients are depleted, niches become occupied with more specialized species (Falk et al., 1998; Hooper et al., 1999). The ability of other commensals to enter these occupied niches will depend on their ability to utilize the nutrients substrates more efficiently and/or to modify the nutrient reservoir to better suit their own metabolic capacities. Therefore, an equilibrium between microbial nutrient utilization and host nutrient production should be achieved, not to be deleterious to each other (Hooper et al., 1999).

In addition to environmental factors such as nutrients, the adult bacterial community is also influenced by host genotype. Indeed, fecal 16S rRNA profiles of the flora of monozygotic twins are more similar than those of unrelated individuals or marital partners (Zoetendal *et al.*, 2001). Nevertheless, despite the variations in the composition of the microbiota between and within individuals, there is a functional stability insuring the basic set of biochemical reactions, such as degradation of carbohydrates, fermentation and synthesis of vitamins. Interestingly, conventionally-raised animals require less calorie intake to maintain their body weight than germ-free counterparts, suggesting the beneficial aid of the microbiota in extracting maximum nutritional value from the diet (Wostmann et al., 1983). It shows that there is a continuous host-microbe-nutrient exchange leading to symbiosis, commensalism or pathogenicity.

Factor such as diet and antibiotic therapy are of undoubted importance in modulating the composition and metabolic activities of the colonic microflora. The greatest changes in species composition occur during the natural process of bacterial colonization in infancy.

Diet is a key factor regulating the sequence of colonization. In breast-fed infants, the intestinal flora is dominated by bifidobacteria, while formula-fed infants have a more diverse flora (Benno et al., 1984; Harmsen et al., 2000). In breast-fed infants, the microflora produces high amounts of acetate and lactate restricting the growth of potential pathogens such as *Escherichia coli* and *Clostridium perfringens* (Wang and Gibson, 1993). In comparison, in formula-fed infants, relatively high amounts of propionate and butyrate are produced. The favoured growth of bifidobacteria in breast-fed infants is likely due to the presence of neutral oligosaccharides with prebiotic effect, in woman milk (Engfer et al., 2000). Alike human milk, the addition of prebiotics (i.e. non-digestible food ingredients) to infant regimen, stimulate the growth of beneficial endogenous bacteria. As an example, feeding infants with galacto- and fructo- oligosaccharides formula significantly increased the number of bifidobacteria (Boehm et al., 2002; Moro et al., 2002).

Finally, a certain number of studies revealed age-related changes in the composition of the human gut microbiota (Mitsuoka et al., 1975). A recent molecular cross-sectional study performed on intestinal microbiota composition from different European countries (Mueller et al., 2006) showed differences in microbiota composition, notably concerning the proportion of bifidobacteria, that may be explained by host specificities or diet-related differences. Additionally, higher proportions of enterobacteria

were found in all elderly volunteers independently of the geographic location.

III.1.c : Metabolism and commensal flora: sugar and lipid metabolism, fat storage, angiogenesis.

As described in the first section of our review for the adipose tissue, the microbiota can be viewed as a true metabolic organ. The main studies that showed microbial contribution to nutrient metabolism has been done by the use of the commensal *Bacteroides thetaiotaomicron* (Hooper et al., 2002). Using genetically-modified bacteria, several genes have been identified that participate in carbohydrate metabolism, such as those encoding SusC-SusF outer membrane proteins, involved in the binding of starch to the bacterial surface allowing its digestion by α-amylases encoded by *sus-A* and *sus-G* genes (D'Elia and Salyers, 1996). These genes are under the regulation of a transcriptional activator (sus-R) that senses maltose or larger oligosaccharides.

The capacity of *B. thetaiotaomicron* to degrade a variety of host-derived glycoconjugates, such as chondroitin sulphate, has also been linked to other genes, such as *csuF* encoding a potential receptor for these glycoconjugates, and *chuR* controlling the expression of the genes involved in the utilization of glycans (Cheng et al., 1992). This is essential since host glycans are critical for *B. thetaiotaomicron* survival in the intestinal ecosystem.

Other host molecules, such as mucins and glycosphingolipids, can also be degraded by bacterial enzymes (Lowe et al., 1998). Altogether, by serving as nutrient sources, these microbe-degraded host glycans establish a mutually beneficial host-bacterial interaction.

In parallel, this symbiotic relationship between host and bacteria also involved microbial fermentation processes. The predominant end-products of bacterial fermentation in the gut are short chain fatty acids, such as acetate, propionate and butyrate. Acetate is taken up primarily by peripheral tissues and can also be utilized by adipocytes for lipogenesis (Bergman, 1990). The intestinal ecosystem also plays a crucial role in the metabolism of lignan, a dietary phytoestrogen coupound from plant origin, which could be involved in colon cancer, atherosclerosis and diabetes. Clavel et al. (2005), recently showed that conversion of dietary lignans results from the catalytic activities of bacteria present in the intestinal tract.

The intestinal microflora also contributes to amino-acid synthesis. Indeed, high concentration of urea are found in the colons of germ-free rats, indicating the key role played by the bacteria in nitrogen recycling in the gut (Moreau et al., 1976). Combining gnotobiotic mouse models with functional genomics, Hooper et al. recently further defined the impact of bacterial gut colonization on host's physiology. Indeed, using micro-arrays and laser capture microdissection, these authors followed the changes in gene expression in gut colonized with each components of the normal microbiota, in comparison to germ-free intestines (Hooper et al., 2001; Hooper et al., 2002; Stappenbeck et al., 2002a). It showed modifications in the expression of genes involved in the processing and absorption of carbohydrates or in the breakdown and absorption of complex dietary lipids. Considering *B. thetaiotaomicron*, that we previously mentioned, its proteome contains 172 glycosyl-hydrolases that are predicted to cleave most glycosidic linkages encountered in human diets (Xu et al., 2003).

Along the same lines Bäckhed et al. (2004), recently reported that germ-free mice re-colonized with normal microbiota rapidly develop a 60% increase in body fat mass associated with insulin-resistance, despite reduced food intake. As expected (Maffei et al., 1995), these mice present increased leptin levels, proportional to the increase of body fat. These studies also revealed that microbiota promotes the absorption of monosaccharides from the gut lumen, resulting in the induction of *de novo* hepatic lipogenesis. Indeed, colonization with microbiota induces significant elevations in the expression of two key enzymes of the *de novo* fatty acid biosynthetic pathway, acetyl-CoA carboxylase (Acc1) and fatty acid synthetase (Fas), as well as gene expression of transcription factors involved in hepatocyte lipogenic responses to insulin and glucose. Moreover, the microbiota also promotes the storage of triglycerides in adipocytes through suppression of intestinal expression of a circulating lipoprotein lipase (LPL) inhibitor: the fasting-induced adipocyte factor (FIAF). Fiaf, also known as angiopoietin-like protein 4, is produced by brown and white fat, liver, and intestine. Quantitative RT-PCR analysis of intestinal Fiaf expression during the postnatal period disclosed that the gene is induced in germ-free mice during the suckling-weaning transition. During this period, the diet switches from lipid/lactose-rich mother's milk to low fat/polysaccharide-rich chow, with coincident expansion of the microbiota and a shift from facultative to obligate anaerobes, such as Bacteroides. This repression is thus consistent with an accompanying augmentation of host lipid absorption. Interestingly, the Zebrafish homolog of mouse Fiaf is also suppressed by the microbiota when germ-free fish are colonized, indicating that this phenomenon has been highly conserved over the course of vertebrate evolution (Rawls et al., 2004).

Therefore, microbial suppression of intestinal Fiaf promotes adiposity and Bäckhed et al. (2004) postulate that increasing Fiaf expression and/or activity may promote leanness, opening new therapeutic strategies for the treatment of adipose-tissue associated pathologies, among which obesity.

In addition to playing a role in adipogenesis and adipose tissue functionality, microbiota plays a key role in constructing the microvascular network by increasing expression of angiogenin-3 in the crypt epithelium, a secreted protein with angiogenic activity, within paneth cells (Hooper et al., 2001). These findings enlarged the participation of microbiota in the whole physiology of an organism to an unexpected role in postnatal development (Stappenbeck et al., 2002b).

To conclude, we will now exemplify selected findings describing the influence of environmental factors on the quality of the intestinal flora. Regarding this, any changes in microbial ecology prompted by western diets, and/or differences in microbial ecology, may impact on the health.

Molecular analysis of the bacterial microbiota based on the 16S rRNA genes have attracted attention as reliable methods to follow the microbial diversity and particularly how it could be affected

in a particular environment (Ducan et al., 2003). First, a recent study showed that short-course antibiotic challenges strongly and long-lastingly modulate bacterial microbiota explaining certain susceptibilities to antibiotic-associated diarrhea (De La Cochetiere et al., 2005). Second, in case of chronic intestinal inflammatory diseases, such as Crohn disease (CD), it was reported that faecal microbiota of patients with CD contains a markedly reduced diversity of Firmicutes, compared with healthy donors (Manichanh et al., 2006). This observation is of crucial importance since the indigenous microflora is considered to be the main factor triggering this inflammatory disease. Indeed, the reduced proportion of Firmicutes may lead to an increase of gram negative bacteria with pro-inflammatory activities. Moreover, some Firmicutes produce large amount of butyrate interfering with the NFkB activation cascade, consequently inhibiting inflammation.

III. 2. Functional food.

III.2.a : Functional food: Historic.

The tenet "Let food be thy medicine and medicine be thy food" espoused by Hippocrates nearly 2,500 years ago, has recently received renewed interest with the emerging concept of "functional foods". This term, first introduced in Japan in the mid-1980's, referred to processed foods containing ingredients that aid specific body functions in addition to being nutritious. The current definition of "Functional foods" is the following : "Foods or dietary components that may provide a health benefit beyond basic nutrition" (International Life Sciences Report, 1999).

The interest in the ability of functional foods to impact on human health has rapidly grown recently, so has accumulated knowledge detailing their beneficial roles. In the last decade of the 20th century, consumers began to view their diets from a radically different vantage point. Our diet is now considered as a first line of defences in the prevention of various chronic diseases of aging ranging from diabetes and obesity to cancer and cardiovascular diseases (Hasler, 2000).

III.2.b : Functional food: Concept.

A large variety of foods provide health-benefits by altering one or more physiologic processes. The ability of specific foods to prevent and/or reduce the severity of symptoms and diseases come from a series of ancient reports. Currently, dozens of physiologically-active functional food components, from plants (i.e. phyto-chemicals) as well as animals (i.e. zoo-chemicals) are under investigation for their potential role in disease prevention and health promotion. Two reports attempted to list the great number of functional components, providing many examples of food having health-promoting properties ((Hasler, 2000), www.eatright.org). Broccoli, carrots, or tomatoes could be considered functional foods since they are rich in well-recognized physiologically active components such as, respectively, sulforaphane, beta carotene, and lycopene. More generally speaking, increased consumption of fruits, vegetables or nutrients naturally rich in soluble fibers, such as oat bran, is associated with reduced risk for cancer or coronary heart disease (Cohen et al., 2003). Similarly, plant-derived sterol and stanol esters and consumption of omega-3 fatty acids mostly originating from fish, have been convincingly described to promote cholesterol reduction and decrease the risk of cardiovascular diseases (FDA Report, 2000).

Finally, fermented-dairy products containing probiotics have also been shown to improve gastro-intestinal health (Sanders and Huis in't Veld, 1999), notably by modulating the endogenous microflora.

III.2.c : Probiotics.

Probiotics are defined as "microorganisms which upon ingestion in certain number exert health-benefits beyond inherent general nutrition" (Guarner and Schaafsma, 1998). Probiotic bacteria, intrinsically GRAS (generally recognized as safe) microorganisms, are mainly belonging to the lactic acid bacteria (LAB) family, and are well known to exert beneficial effects in human or animal health.

First, positive effects of LAB have been reported on intestinal functions. The more substantiated effect concerns the improvement on the digestion of lactose (Kolars et al., 1984). Probiotics have also a stimulatory effect on the colonic reabsorption of water and sodium, *via* short chain fatty acids, particularly butyrate, along with that of calcium, magnesium, iron and zinc (Scholz-Ahrens et al., 2001).

Certain strains of bacteria act directly on bile acids through Bile Salt Hydrolase (BSH) activity (Moser et al., 2001). Most of the *Lactobacillus* isolates from human and dairy products possess genes encoding BSH activities (*cbsH*) and also conjugated bile salt transporters (*cbsT1*, *cbsT2*) (Elkins et al., 2001; Elkins and Savage, 2003). Control of cholesterol through oral live bacterial cell-therapy is based on the demonstration that certain natural *lactobacilli* can significantly lower serum cholesterol due to BSH activities (De Smet et al., 1994; Anderson and Gilliland, 1999; Taranto et al., 2000). More recently, Jones *et al.* (2004) showed the potential of artificial cell microencapsulated genetically engineered *Lactobacillus plantarum* for bile acids deconjugation to lower cholesterol. Animal studies have confirmed the *in vivo* cholesterol-lowering effects of selected probiotic strains (Chiu et al., 2005). Milk diets containing *Bifidobacterium* have been shown to improve serum lipids in rats as well as in humans with moderate hypercholesterolemia, suggesting a potential use of probiotics in lowering serum cholesterol (Roller, 2004). Same type of study performed with *Bacillus polyfermenticus* in rats fed with high fat and high cholesterol diet showed significant health benefits occurring via the modulation of physiologic functions including various arthrogenic lipid profiles and antioxidants in hypercholestrolemia (Paik, 2005). Moreover, Bleau *et al.* (2005) recently suggested that selected lactobacilli isolates could reduce Th1-mediated mucosal inflammation by reducing leptin release. Only few human nutritional studies have been designed to assess the effect of probiotics consumption on the composition of the intestinal microbiota. The availability of the genome sequences and post-genomics tools regarding such microorganisms, is opening new issues to investigate the functions of these bacteria in the gut. Using such approach, we recently

participated to the identification of genes of *Lactobacillus plantarum* whose expression was induced during passage of these bacteria through the gastrointestinal tract. Interestingly, 9 of these 72 genes encode sugar-related functions, whereas others are involved in acquisition and synthesis of amino acids, nucleotides, cofactors and vitamins (Bron, 2004).

In addition, regular intake of probiotic bacteria contributes to immune homeostasis by altering microbial balance or by interacting with the gut immune system, explaining their potential effect in gastro-intestinal diseases. Probiotics have proven benefits in treatment or prevention of certain type of diarrhea (Arvola et al., 1999), inflammatory bowel diseases (Gionchetti et al., 2000; Fedorak and Madsen, 2004), some cancers (Takahashi et al., 2001), food allergy and atopic eczema in children (Kalliomaki et al., 2001). These beneficial effects can be exerted through different means, such as production of anti-microbial metabolites, competitive exclusion of enteric pathogens, or neutralization of dietary carcinogens.

The protective effects of probiotics could also be explained by their role in the modulation of mucosal immune responses. Indeed we, and others, showed that probiotics present distinct strain-specific immunomodulatory capacities *in vitro* (Hessle et al., 1999; Maassen et al., 2000; Mercenier et al., 2004) which can be closely correlated with their *in vivo* anti-inflammatory potential. Interestingly, the anti-inflammatory effects of lactobacilli observed after either oral or systemic administration (Foligne et al., 2005; Sheil et al., 2004), suggest that the protective mechanisms might involve regulatory-cell populations. Similarly, recent studies reported that a defined probiotic mixture ameliorates murine colitis by inducing regulatory-T cells (Di Giancinto et al., 2005) and we recently showed that selected strains are able to induce tolerogenic dendritic cells.

Finally, probiotics, thanks to their GRAS characteristics associated with their high resistance to the gastric barrier, have been genetically engineered as tools for the delivery of antigens or therapeutic molecules (Robinson et al., 1997; Steidler et al., 2000; Grangette et al., 2001). Nevertheless and obviously, there are many scientific, political and social barriers to allow the introduction of such genetically modified organisms.

Changing lifestyles and dietary patterns over the last 20 years have conspired to increase a number of imbalances. Factors such as advanced age, diabetes, overweight and obesity are considered as risk factors for many diseases. As we evoked above, the combined supplementation of bioactive fibers and probiotics to our diet, could decrease several of these risk factors (Roberfroid, 2000; Bengmark, 2005).

Thereby, in the field of nutritional science, the current challenge is to supply fundamental and concrete findings to provide efficient and safe strains to consumers (Gorbach, 2002). In parallel, functional food legislations are being organized worldwide and a special issue recently published (Bagchi, 2006) provides a sequential description of the main regulatory rules. In the United States, the Food and Drug Administration's (FDA) involvement with functional foods expanded in recent years, however, the regulation concerning this type of nutrient and their associated health-claims remains confused (Bagchi, 2006). Similarly in Japan, the Foods for Specified Health Uses (FOSHU) and in Europe, the International Life Sciences Institute (ILSI, http://europe.ilsi.org/passclaim) have defined the general principles and requirements of food laws. The PASSCLAIM document delivers criteria to assess the scientific support for claims on foods (Aggett, 2005).

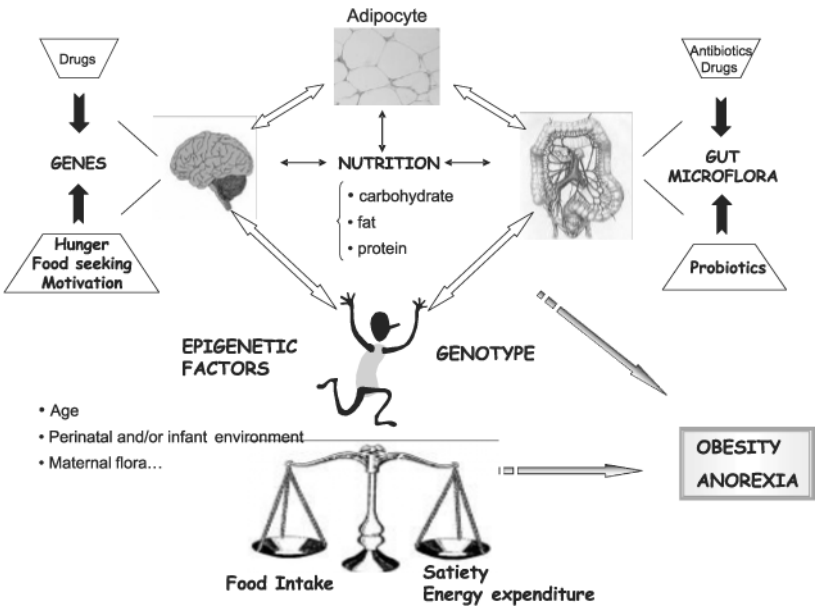
A better understanding of how diet influences individual's genetic potential, overall performance and susceptibility to disease together with a general legislation regulating the use of both dietary supplements and functional foods, will have enormous implications for our society (Milner, 2000).

IV. Overall conclusion.

In this review, we attempted to summarize selected aspects of the regulation of energy homeostasis. Since obesity and its numerous related-disorders are now harmfully blowing up in our industrialized societies, identification and deciphering of the main actors controlling food intake turn out to be an urgent priority considering their enormous toll on human health.

We mainly took into consideration the links existing between the so-to-speak "brains" (*i.e.* the central nervous system and the enteric nervous system) and the white adipose tissue emphasizing both genes and nutrition (Figure 3).

FIGURE 3. Factors involved in the regulation of genes devoted to the control of nutrition state.



First, we reported how the formation and functionality of adipose cells is strongly modulated by our diet, taking as examples the extreme cases of calorie restriction and diet-induced obesity both regulating the expression of key genes controlling the adipogenesis process, like PPAR-γ.

Second, we described where and how the central nervous system integrates peripheral signals from the adipose tissue and/or the gastro-intestinal tract according to the nutritional status. We showed that adipocyte- or enteric- derived signals, such as respectively leptin or ghrelin, target the brain in order to ensure a suitable response to any nutritional challenge. Once again, we gave examples of hypothalamic genes highly responsive to nutrient variations.

Last, after a short description of the intestinal commensal flora ranging from its composition to its importance in immune surveillance, we enlarged on how nutrition modified this perfectly well balanced ecosystem. Finally, since consumers worldwide become more health conscious, we end up this third part by presenting the general aspects on functional food and the current claims and perspectives. To conclude, with this review we aimed to help rounding out the picture of how nutrition impacts energy homeostasis.

REFERENCES

Aggett, P.J., Antoine, J.-M., Asp, N.-G., Bellisle, F., Contor, L., Cummings, J.H., Howlet, J., Müller, D.J.G., Persin, C., Pijls, L.T.J., Rechkemmer, G., Tuijtelaars, S. and Verhagen, H. (2005) PASSCLAIM. Process for the assessement of scientific support for claims on foods. Consensus criteria. *European Journal of Nutrition* **44**(supll 1), I1-I30.

Ahima, R.S. (2005) Central actions of adipocyte hormones. *Trends in Endocrinology and Metabolism* **16**, 307-13.

Al-Hasani, H. and Joost, H.G. (2005) Nutrition-/diet-induced changes in gene expression in white adipose tissue. *Best Practice and Research Clinical Endocrinoly and Metabolism* **19**, 589-603.

Anand, B.K. and Brobeck, J.R. (1951) Localization of a "feeding center" in the hypothalamus of the rat. *Proceedings of the Society of Experimental Biological Medicine* **77**, 323-324.

Anderson, J.W. and Gilliland, S.E. (1999) Effect of fermented milk (yogurt) containing lactobacillus acidophilus L1 on serum cholesterol in hypercholesterolemic humans. *Journal of the American College of Nutrition* **18**, 43-50.

Arvola, T., Laiho, K., Torkkeli, S., Mykkanen, H., Salminen, S., Maunula, L. and Isolauri, E. (1999) Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. *Pediatrics* **104**, e64.

Asakawa, A., Inui, A., Kaga, T., Yuzuriha, H., Nagata, T., Ueno, N., Makino, S., Fujimiya, M., Niijima, A., Fujino, M.A. and Kasuga, M. (2001) Ghrelin is an appetite stimulatory signal from stomach with structural resemblance to motilin. *Gastroenterology* **120**, 337-345.

Attoub, S., Levasseur, S., Buyse, M., Goiot, H., Laigneau, J.-P., Moizo, L., Hervatin, F., Le Marchand-Brustel, Y., Lewin, J.M. and Bado, A. (1999) Physiological role of cholecystokinin B/gastrin receptor in leptin secretion. *Endocrinology* **140**, 4406-4410.

Aubert, J., Saint-Marc, P., Belmonte, N., Dani, C., Negrel, R. and Ailhaud, G. (2000) Prostacyclin IP receptor up-regulates the early expression of C/EBP-beta and C/EBP-delta in preadipose cells. *Molecular and Cellular Endocrinology* **160**, 149-156.

Auwerx, J. and Staels, B. (1998) Leptin. *Lancet* **351**, 737-42.

Bäckhed, F., Ding, H., Wang, T., Hooper, L.V., Koh, G.Y., Nagy, A., Semenkovich, C.F. and Gordon, J.I. (2004) The gut microbiota as an environmental factor that regulates fat storage. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 15718-15723.

Bado, A., Levasseur, S., Attoub, S., Kermorgant, S., Laigneau, J.-P., Bortoluzzi, M.N., Moizo, L., Lehy, T., Guerre-Millo, M., Le Marchand-Brustel, Y. and Lewin, M.J. (1998) The stomach is a source of leptin. *Nature* **394**, 790-793.

Bagchi, D. (2006) Nutraceuticals and functional foods regulations in the United States and around the world. *Toxicology* **221**, 1-3.

Bai, F.L., Yamano, M., Shiotani, Y., Emson, P.C., Smith, A.D., Powell, J.F. and Tohyama, M. (1985) An arcuato-paraventricular and -dorsomedial hypothalamic neuropeptide Y-containing system which lacks noradrenaline in the rat. *Brain Research* **331**, 172-175.

Banks, W.A., DiPalma, C.R. and Farrell, C.L. (1999) Impaired transport of leptin across the blood-brain barrier in obesity. *Peptides* **20**, 1341-1345.

Barak, Y., Nelson, M.C., Ong, E.S., Jones, Y.Z., Ruiz-Lozano, P., Chien, K.R., Koder, A. and Ewans, R.M. (1999) PPAR gamma is required for placental, cardiac and adipose tissue development. *Molecular Cell* **4**, 585-595.

Barrachina, M.D., Martinez, V., Wang, L., Wei, J.Y. and Tache, Y. (1997) Synergistic interaction between leptin and cholecystokinin to reduce short-term food intake in lean mice. *Proceedings of the National Academy of Sciences of the United States of America* **94**, 10455-10460.

Bastard, J.P., Jardel, C., Bruckert, E., Blondy, P., Capeau, J., Laville, M., Vidal, H. and Hainque, B. (2000) Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *Journal of Clinical Endocrinology and Metabolism* **85**, 3339-3342.

Baura, G.D., Foster, D.M., Porte, D.Jr, Kahn, S.E., Bergman, R.N., Cobelli, C. and Schwartz, M.W. (1993) Saturable transport

of insulin from plasma into the central nervous system of dogs in vivo. A mechanism for regulated insulin delivery to the brain. *Journal of Clinical Investigation* **92**, 1824-1830.

Bengmark, S. (2005) Synbiotics and the mucosal barrier in critically ill patients. *Current Opinion in Gastroenterology* **21**, 712-716.

Benno, Y., Sawaka, K. and Mitsuoka, T. (1984) The intestinal microflora of infants: composition of fecal flora in breast-fed and bottel-fed infants. *Microbiology and Immunology* **28**, 975-986.

Bergman, E.N. (1990) Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. *Physiological Reviews* **70**, 567-590.

Berthoud, H.R. (2002) Multiple neural systems controlling food intake and body weight. *Neuroscience and Biobehavioral Review* **26**, 393-428.

Bittencourt, J.C., Presse, F., Aria, C., Pet, C., Vaughan, J., Nahon, J.L., Vale, W. and Sawchenko, P.E. (1992) The melanin-concentrating hormone system of the rat brain: an immuno- and hybridization histochemical characterization. *Journal of Comparative Neurology* **319**, 218-245.

Bjorbaek, C., Elmquist, J.K., Frantz, J.D., Shoelson, S.E. and Flier, J.S. (1998) Identification of SOCS-3 as a potential mediator of central leptin resistance. *Molecular Cell* **1**, 619-625.

Blanchette-Mackie, .E.J. and Scow, R.O. (1981) Lipolysis and lamellar structures in white adipose tissue of young rats: lipid movement in membranes. *Journal of Ultrastructural Research* **77**, 295-318.

Blüher, M., Michael, M.D., Peroni, O.D., Ueki, K., Carter, N., Kahn, B.B. and Kahn, C.R. (2002) Adipose tissue selective insulin receptor knockout protects against obesity and obesity-related glucose intolerance. *Developmental Cell* **3**, 25-38.

Blüher, M. (2005) Transgenic animal models for the study of adipose tissue biology. *Best Practice & Research Clinical Endocrinology & Metabolism* **19**, 605-623.

Boehm, G., Lidestri, M., Casetta, P., Jelinek, J., Negretti, F., Stahl, B. and Marini, A. (2002) Supplementation of a bovine milk formula with an oligosaccharide mixture increases counts of faecal bifidobacteria in preterm infants. *Archives of Diease in Childhood. Fetal and Neonatal Edition* **86**, F178-81.

Bouret, S.G., Draper, S.J. and Simerly, R.B. (2004a) Formation of projection pathways from the arcuate nucleus of the hypothalamus to hypothalamic regions implicated in the neural control of feeding behavior in mice. *Journal of Neuroscience* **24**, 2797-2805.

Bouret, S.G., Draper, S.J. and Simerly, R.B. (2004b) Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science* **304**, 108-110.

Bowers, C.Y. (2001) Unnatural growth hormone-releasing peptide begets natural ghrelin. *Journal of Clinical Endocrinology and Metabolism* **86**, 1464-1469.

Bron, P.A., Grangette, C., Mercenier, A., de vos W.M. and Kleerebezem, M. (2004) Identification of *Lactobacillus plantarum* genes that are induced in the gastrointestinal tract of mice. *Journal of Bacteriology* **186**, 5721-5729.

Cammisotto, P.G., Renaud, C., Gingras, D., Delvin, E., Levy, E. and Bendayan, M. (2005) Endocrine and exocrine secretion of leptin by the gastric mucosa. *Journal of Histochemistry and Cytochemistry* **53**, 851-860.

Carlberg, M., Gundlach, A.L., Mercer, L.D. and Beart, P.M. (1992) Autoradiographic Localization of Cholecystokinin A and B Receptors in Rat Brain Using [125I]d-Tyr25 (Nle28,31)-CCK 25 - 33S. *European Journal of Neuroscience* **4**, 563-573.

Cao, Z., Umek, R.M. and McKnight, S.L. (1991) Regulated expression of three C/EBP isoforms during adipose conversion of 3T3-L1 cells. *Genes and Development* **5**, 1538-1552.

Caro, J.F., Kolaczynski, J.W., Nyce, M.R., Ohannesian, J.P., Opentanova, I., Goldman, W.H., Lynn, R.B., Zhang, P.L., Sinha, M.K. and Considine, R.V. (1996) Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. *Lancet* **348**, 159-161.

Case, C.C., Jones, P.H., Nelson, K., O'Brian Smith, E. and Ballantyne, C.M. (2002) Impact of weight loss on the metabolic syndrome. *Diabetes, Obesity and Metabolism* **87**, 407-414.

Cederberg, A., Gronning, L.M., Ahren, B., Tasken, K., Carlsson, P. and Enerback, S. (2001) FOXC2 is a winged helix gene that counteracts obesity, hypertriglyceridemia, and diet-induced insulin-resistance. *Cell* **106**, 563-573.

Chen, M., Yang, Y.K., Loux, T.J., Georgeson, K.E and Harmon, C.M. (2006) The role of hyperglycemia in FAT/CD36 expression and function. *Pediatric Surgery International* [Epub ahead of print].

Cheng, Q., Hwa, V. and Salyers, A.A. (1992) A locus that contributes to colonization of the intestinal tract by Bacteroides thetaiotaomicron contains a single regulatory gene (chuR) that links two polysaccharide utilization pathways. *Journal of Bacteriology* **174**, 7185-7193.

Cheung, C.C., Clifton, D.K. and Steiner, R.A. (1997) Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus. *Endocrinology* **138**, 4489-4492.

Chiu, C.-H., Lu, T.-Y., Tseng, Y.-Y. and Pan, T.-M. (2005) The effects of Lactobacillus-fermented milk on lipid metabolism in hamsters fed on high-cholesterol diet. *Applied Microbiology and Biotechnology* **71**, 238-245.

Clavel, T., Henderson, G., Alpert, C.A., Philippe, C., Rigottier-Gois, L., Dore, J. and Blaut, M. (2005) Intestinal bacterial communities that produce active estrogen-like compounds enterodiol and enterolactone in humans. *Applied and Environmental Microbiology* **71,** 6077-6085.

Cohen, R., Bouquier, D., Biot-Laporte,., Vermeulen, E., Claustrat, B., Cherpin, M.H., Cabrera, P., Guidetti, P., Ferry, S. and Bizollon, C.A. (1986) Pituitary stimulation by combined administration of four hypothalamic releasing hormones in normal men and patients. *Journal of Clinical Endocrinology and Metabolism* **62**, 892-898.

Cohen, J.F., Kristal, R.A. and Stanford, J.K. (2003) Cholesterol-lowering effects of dietary fiber: A meta-analysis. *Journal of the National Cancer Institute* **92**, 61-68.

Coleman, D.L. and Hummel, K.P. (1969) Effects of parabiosis of normal with genetically diabetic mice. *American Journal of Physiology* **217**, 1298-1304.

Coleman, D.L. and Hummel, K.P. (1973) The influence of genetic background on the expression of the obese (Ob) gene in the mouse. *Diabetologia* **9**, 287-293.

Couceyro, P.R., Koylu, E.O. and Kuhar, M.J. (1997) Further studies on the anatomical distribution of CART by in situ hybridization. *Journal of Chemical Neuroanatomy* **12**, 229-241.

Cummings, D.E., Purnell, J.Q., Frayo, R.S., Schmidova, K., Wisse, B.E. and Weigle, D.S. (2001) A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. *Diabetes* **50**, 1714-1719.

Cummings, D.E., Weigle, D.S., Frayo, R.S., Breen, P.A., Ma, M.K., Dellinger, E.P. and Purnell, J.Q. (2002) Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *New England Journal of Medicine* **346**, 1623-1630.

Dandona, P., Weinstock, R., Thusu, K., Abdel-Rahma, E., Aljada, A. and Wadden, T. (1998) Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss. *Journal of Clinical Endocrinology and Metabolism* **83**, 2907-2910.

Date, Y., Toshinai, K., Koda, S., Miyazato, M., Shimbara, T., Tsuruta, T., Niijima, A., Kangawa, K. and Nakazato, M. (2005) Peripheral interaction of ghrelin with cholecystokinin on feeding regulation. *Endocrinology* **146**, 3518-3525.

Davis, M. (2000) The role of the amygdala in conditioned and unconditioned fear and anxiety. *In*: Aggleton JP, editor. The Amygdala. Oxford: Oxford University Press, pp. 213-288.

Debons, A.F., Krimsky, I., Maayan, M.L., Fani, K. and Jemenez, F.A. (1977) Gold thioglucose obesity syndrome. *Federation Proceedings* **36**, 143-147.

De La Cochetiere, M.F., Durand, T., Lepage, P., Bourreille, A., Galmiche, J.P. and Dore, J. (2005) Resilience of the dominant human fecal microbiota upon short-course antibiotic challenge. *Journal of Clinical Microbiology* **43**, 5588-5592.

De Lece, L., Kilduff, T.S., Peyron, C., Gao, ., Foye, P.E., Danielson, P.E., Fukuhara, C., Battenberg, E.L., Gautvik, V.T., Bartlett, F.S. 2nd, Frankel, W.N., van den Pol, A.N., Bloom, F.E., Gautvik, K.M. and Sutclif, J.G. (1998) The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proceedings of the National Academy of Sciences of the United States of America* **95**, 322-327.

D'Elia, J.N., and Salyer, A.A. (1996) Contribution of a neopullulanase, a pullulanase, and an alpha-glucosidase to growth of Bacteroides thetaiotaomicron on starch. *Journal of Bacteriology* **178**, 7173-7179.

De Smet, I., Van Hoorde, L., De Sayer, M., Vande, W.M. and Verstraete, W. (1994) In vitro study of bile salt hydrolase (bsh) activity on bsh isogenic *Lactobacillus plantarum* 80 strains and estimation of cholesterol lowering through enhanced bsh activity. *Microbial Ecology in Helath and Disease* **7**, 315-329.

Dhillon, H., Zigman, J.M., Ye, C., Le, C.E., McGovern, R.A., Tang, V., Kenny, C., Christiansen, L.M., White, R.D., Edelstein, E.A., Coppari, R., Balthasar, N., Cowley, M.A., Chua, S. Jr, Elmquist, J.K. and Lowell, B.B. (2006) Leptin directly activates SF1 neurons in the VMH, and this action by leptin is required for normal body-weight homeostasis. *Neuron* **49**, 191-203.

Dickson, S.L. and Luckma, S.M. (1997) Induction of c-fos messenger ribonucleic acid in neuropeptide Y and growth hormone (GH)-releasing factor neurons in the rat arcuate nucleus following systemic injection of the GH secretagogue, GH-releasing peptide-6. *Endocrinology* **138**, 771-777.

Di Giacinto, C., Marinaro, M., Sanchez, M., Strober, W. and Boirivant, M. (2005) Probiotics ameliorate recurrent Th1-mediated murine colitis by inducing IL-10 and IL-10-dependent TGF-beta-bearing regulatory cells. *Journal of Immunology* **174**, 3237-3246.

Duncan, S.H., Scott, K.P., Ramsay, A.G., Harmsen, H.J., Welling, G.W., Stewart, C.S. and Flint, H.J. (2003) Effects of alternative dietary substrates on competition between human colonic bacteria in an anaerobic fermentor system. *Applied and Environmental Microbiology* **69**, 1136-1142.

Eckburg, P.B., Bik, E.M., Bernstein, C.N., Purdom, E., Dethlefsen, L., Sargent, M., Gill, S.R., Nelson, K.E. and Relman. (2005) Diversity of the human intestinal microbial flora. *Science* **308**, 1635-1638.

Edholm, O.G. (1997) Energy balance in man studies carried out by the Division of Human Physiology, National Institute for Medical Research. *Journal of Human Nutrition* **31**, 413-4131.

Egert, M., de Graaf, A.A., Smidt, H., de Vos, W.M. and Venema, K. (2006) Beyond diversity: functional microbiomics of the human colon. *Trends in Microbiology* **14**, 86-91.

Elias, C.F., Saper, C.B., Maratos-Flier, E., Tritos, N.A., Lee, C., Kelly, J., Tatro, J.B., Hoffman, G.E., Ollmann, M.M., Barsh, G.S., Sakurai, T., Yanagisawa, M, and Elmquist, J.K. (1998) Chemically defined projections linking the mediobasal hypothalamus and the lateral hypothalamic area. *Journal of Comparative Neurology* **402**, 442-459.

Elkins, C.A., Moser, S.A. and Savage, D.C. (2001) Genes encoding bile salt hydrolases and conjugated bile salt transporters in *Lactobacillus johnsonii* 100-100 and other *Lactobacillus* species. *Microbiology* **147**, 3403-3412.

Elkins, C.A. and Savage, D.C. (2003) CbsT2 from *Lactobacillus johnsonii* 100-100 is a transport protein of the major facilitator superfamily bile acid antiport. *Journal of Molecular Microbiology and Biotechnology* **6**, 76-87.

Elmquist, J.K., Ahima, R.S., Maratos-Flier, E., Flier, J.S. and Saper, C.B. (1997) Leptin activates neurons in ventrobasal hypothalamus and brainstem. *Endocrinology*138:839-842.

Elmquist, J.K., Bjorbaek, C., Ahima, R.S., Flier, J.S. and Saper, C.B. (1998) Distributions of leptin receptor mRNA isoforms in the rat brain. *Journal of Comparative Neurology* **395**, 535-547.

Elmquist, J.K., Elias, C.F. and Sape, C.B. (1999) From lesions to leptin: hypothalamic control of food intake and body weight. *Neuron* **22**, 221-232.

Engfer, M.B., Stahl, B., Finke, B., Sawatzki, G. and Daniel, H. (2000) Human milk oligosaccharides are resistant to enzymatic hydrolysis in the upper gastrointestinal tract. *American Journal of Clinical Nutrition* **71**, 1589-1596.

Fajas, L., Schoonjans, K., Gelman, L., Kim, J.B., Najib, J., Martin, G., Fruchart, J.-C., Brigg, M., Spiegelman, B.M. and Auwerx, J. (1999) Regulation of peroxisome proliferator-activated receptor-gamma expression by adipocyte differentiation and determination factor-I/sterol regulatory element-binding protein I: implications for adipocyte differentiation and metabolism. *Molecular and Cellular Biology* **19**, 5495-5503.

Falk, P.G., Hooper, L.V., Midtvedt, T. and Gordon, J.I. (1998) Creating and maintaining the gastrointestinal ecosystem: what we know and need to know from gnotobiology. *Microbiology and Molecular Biology Reviews* **62**, 1157-1170.

Fan, W., Boston, B.A., Kesterson, R.A., Hruby, V.J. and Cone, R.D. (1997) Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. *Nature* **385**, 165-168.

Farooqi, I.S., Keogh, J.M., Kamath, S., Jones, S., Gibson, W.T., Trussell, R., Jebb, S.A., Lip, G.Y. and O'Rahilly, S. (2001) Partial leptin deficiency and human adiposity. *Nature* **414**, 34-35.

Farooqi, I.S., Matarese, G., Lord, G.M., Keogh, J.M., Lawrence, E., Agwu, C., Sanna, V., Jebb, S.A., Perna, F. and Fontana, S. (2002) Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *Journal of Clinical Investigation* **110**, 1093-1103.

Faust, I.M., Johnson, P.R., Stern, J.S. and Hirsch, J. (1978) Diet-induced adipocyte number increase in adult rats: a new model of obesity. *American Journal of Physiology* **235**, E279-E286.

Faust, I.M., Miller, W.H., Sclafani, A., Aravich, P.F., Triscari, J. and Sullivan, A.C. (1984) Diet-dependent hyperplastic growth of adipose tissue in hypothalamic obese rats. *American Journal of Physiology* **247**, R1038-R1046.

Fedorak, R.N. and Madsen, K.L. (2004) Probiotics and the management of inflammatory bowel disease. *Inflammatory Bowel Diseases* **10**, 286-299.

Fève, B. (2005) Adipogenesis: cellular and molecular aspects. *Best Practice & Research Clinical Endocrinology & Metabolism* **19**, 483-499.

FAD Report Department of Health and Human Services, U. F. a. D. A. (2000) Food labeling: Health claims; plant sterol/stanol esters and coronary heart disease. *Interim final rule Federal Reglementation* **65**, 54686-54739.

Foligne, B., Grangette, C. and Pot, B. (2005) Probiotics in IBD: mucosal and systemic routes of administration may promote similar effects. *Gut* **54**, 727-728.

Fox, E.A., Phillips, R.J., Baronowsky, E.A., Byerly, M.S., Jones, S. and Powley, T.L. (2001) Neurotrophin-4 deficient mice have a loss of vagal intraganglionic mechanoreceptors from the small intestine and a disruption of short-term satiety. *Journal of Neuroscience* **21**, 8602-8615.

Friedman, J.M. (2003) A war on obesity, not the obese. *Science* **299**, 856-858.

Fu, Y., Luo, N., Klein, R.L. and Garvey, V.T. (2005) Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation. *Journal of Lipid Research* **46**, 1369-1379.

Gimble, J.M., Wanker, F., Wang, G.S., Bass, H., Wu, X., Kelly, K., Yancopulos, G.D. and Hill, M.R. (1994) Regulation of bone marrow stromal cell differentiation by cytokines whose receptors share the gp130 protein. *Journal of Cellular Biochemistry* **54**, 122-133.

Gionchetti, P., Rizzello, F., Venturi, A., Brigidi, P., Matteuzzi, D., Bazzocchi, Poggioli, G., Miglioli, M. and Campieri, M. (2000)

Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* **119**, 305-309.

Gomez-Ambrosi, J., Catalan, V., Diez-Caballer, A., Martinez-Cruz, L.A., Gil, M.J., Garcia-Foncillas, J., Cienfuegos, J.A., Salvador, J., Mato, J.M. and Frubeck, G. (2004) Gene expression profile of omental adipose tissue in human obesity. *Faseb Journal* **18**, 215-217.

Gorbach, S.L. (2002) Probiotics in the third millennium. *Digestive Liver Diseases* **34**, S2-S7.

Grangette, C., Müller-Alouf, H., Goudercourt, D., Geoffroy, M.-C., Turneer, M. and Mercenier, A. (2001) Mucosal immune responses and protection against tetanus toxin after intranasal immunization with recombinant *Lactobacillus plantarum. Infection and Immunity* **69**, 1547-1553.

Greenberg, A.S. and Obin, M.S. (2006) Obesity and the role of adipose tissue in inflammation and metabolism. *American Journal of Clinical Nutrition* **83**, 461S-465S.

Gregoire, F.M., Smas, C.M. and Sul, H. (1998) Understanding adipocyte differentiation. *Physiological Reviews* **78**, 783-809.

Griffin, E., Re, A., Hamel, N., Fu, C., Bush, H., McCaffrey, T. and Asch, AS. (2001) A link between diabetes and atherosclerosis: Glucose regulates expression of CD36 at the level of translation. *Nature Medicine* **7**, 840-846.

Guarente, L. (2005) Calorie restriction and SIR2 genes-Towards a mechanism. *Mechanisms of Ageing and Development* **126**, 923-928.

Guarner, F., and Schaafsma, G.J. (1998) Probiotics. *International Journal of Food Microbiology* **39**, 237-238.

Guilmeau, S., Buyse, M., Tsocas, A., Laigneau, J.-P. and Bado, A. (2003) Duodenal leptin stimulates cholecystokinin secretion : evidence of a positive leptin-cholecystokinin feedback loop. *Diabetes* **52**, 1664-1672.

Gurnell, M., Savage, D.B., Chatterjee, V.K. and O'Rahilly, S. (2003) The metabolic syndrome : peroxisome proliferator-activated receptor gamma and its therapeutic modulation. *Journal of Clinical Endocrinology and Metabolism* **88**, 2412-2421.

Hahn, T.M., Breininger, J.F., Baskin, D.G. and Schwartz, M.W. (1998) Coexpression of Agrp and NPY in fasting-activated hypothalamic neurons. *Nature Neuroscience* **1**, 271-272.

Halaas, J.L., Gajiwala, K.S., Maffe, M., Cohen, S.L., Chait, B.T., Rabinowitz, D., Lallone, R.L., Burley, S.K. and Friedman, J.M. (1995) Weight-reducing effects of the plasma protein encoded by the *obese* gene. *Science* **269**, 543-546.

Harmsen, H.J., Wildeboer-Veloo, A.C., Raangs, G.C., Wagendorp, A.A., Klijn, N., Bindels, J.G. and Welling, G.W. (2000) Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. *Journal of Pediatric Gastroenterology and Nutrition* **30**, 61-67.

Hasler, C.M. (2000) The changing face of functional foods. *Journal of the American College of Nutrition* **19**, 499S-506S.

Hayek, T., Hussein, K., Aviram, M., Coleman, R., Keidar, S., Pavoltzky, E. and Kaplan, M. (2005) Macrophage foam-cell formation in streptozotocin-induced diabetic mice: stimulatory effect of glucose. *Atherosclerosis* **183**, 25-33.

Hessle, C., Hanson, L.A. and Wold, A.E. (1999) Lactobacilli from human gastrointestinal mucosa are strong stimulators of IL12 production. *Clinical and Experimental Immunology* **116**, 276-282.

Hetherington, A.W. and Ranson, S.W. (1940) Hypothalamic lesions and adiposity in the rat. *Anatomical Record* **78**, 149-172.

Higami, Y. and Pugh, T.D. (2004) Adipose tissue energy metabolism: altered gene expression profile of mice subjected to long-term calorie-restriction. *Faseb Journal* **18**, 415-417.

Hooper, L.V., Xu, J., Falk, P.G., Midtvedt, T. and Gordon, J.I. (1999) A molecular sensor that allows a gut commensal to control its nutrient foundation in a competitive ecosystem. *Proceedings of the National Academy of Sciences of the United States of America* **96**, 9833-9838.

Hooper, L.V., Wong, M.H., Thelin, A., Hansson, L., Falk, P.G. and Gordon, J.I. (2001) Molecular analysis of commensal host-microbial relationships in the intestine. *Science* **291**, 881-884.

Hooper, L.V., Midtvedt, T. and Gordon, J.I. (2002) How host-microbial interactions shape the nutrient environment of the mammalian intestine. *Annual Review of Nutrition* **22**, 283-307.

Ibrahimi, A. and Abumrad, N.A. (2002) Role of CD36 in membrane transport of long-chain fatty acids. *Current Opinion in Clinical Nutrition and Metabolic Care* **5**, 139-145.

International Life Sciences Institute North America Food Component Reports. (1999) *Critical Reviews in food science and nutrition* **39**, 203-316.

Jia, H.G., Rao, Z.R. and Shi, J.W. (1997) Evidence of gamma-aminobutyric acidergic control over the catecholaminergic projection from the medulla oblongata to the central nucleus of the amygdala. *Journal of Comparative Neurology* **381**, 262-281.

Jones, M.L., Chen, H., Ouyang, W., Metz, T. and Parkash, S. (2004) Microencapsulated genetically engineered lactobacillus plantarum 80 (pCBH1) for bile acid deconjugation and its implication in lowering cholesterol. *Journal of Biomedicine and Biotechnology* **1**, 61-69.

Kalliomaki, M., Salminen, S., Arvilommi H., Kero, P., Koskinen, P and Isolauri, E. (2001) Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* **357**, 1076-1079.

Kamegai, J., Tamura, H., Shimizu, T., Ishi, S., Sugihara, H. and Wakabayashi, I. (2000) Central effect of ghrelin, an endogenous growth hormone secretagogue, on hypothalamic peptide gene expression. *Endocrinology* **141**, 4797-4800.

Kamphuis, M.M., Mela, D.J. and Westerterp-Plantenga, M.S. (2003) Diacylglycerols affect substrate oxidation and appetite in humans. *American Journal of Clinical Nutrition* **77**, 1133-1139.

Kannel, W.B., Cupples, L.A., Ramaswami, R., Stokes, J. 3rd, Kreger, B.E. and Higgin, M. (1991) Regional obesity and risk of cardiovascular disease ; the Framingham study. *Journal of Clinical Epidemiology* **44**, 183-190.

Keesey, R.E., Mitchel, J.S. and Kemnitz, J.W. (1979) Body weight and body composition of male rats following hypothalamic lesions. *American Journal of Physiology* **237**, R68-R73.

Kelly, D., Campbell, J.I., King, T.P., Grant, G., Jansson, A.E., Coutts, A.G., Pettersson, S. and Conway, S. (2004) Commensal anaerobic gut bacteria attenuate inflammation by regulating nuclear-cytoplasmic shuttling of PPAR-gamma and RelA. *Nature Immunology* **5**, 104-112.

Kennedy, G.C. (1953) The role of depot fat in the hypothalamic control of food intake in the rat. *Proceedings of the Royal Society of London. Series B. Biological Sciences* **140**, 578-596.

Kim, J.B., Wright, H.M., Wright, M. and Spiegelman, B.M. (1998) ADD1/SREBP1 activates PPAR-gamma through the production of endogenous ligand. *Proceedings of the National Academy of Sciences of the United States of America* **98**, 4333-4337.

Kim, K.H., Lee, K., Moon, Y.S. and Su, H.S. (2001) A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte differentiation. *Journal of Biological Chemistry* **276**, 11252-11256.

King, B.M., Rossiter, K.N., Stines, S.G., Zaharan, G.M., Cook, J.T., Humphries, M.D. and York, D.A. (1998) Amygdaloid-lesion hyperphagia: impaired response to caloric challenges and altered macronutrient selection. *American Journal of Physiology* **275**, R485-R493.

King, B.M., Cook, J.T., Rossiter, K.N. and Rollins, B.L. (2003) Obesity-inducing amygdala lesions: examination of anterograde degeneration and retrograde transport. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **284**, R965-R982.

Knouff, C. and Auwerx, J. (2004) Peroxisome proliferator-activated receptor gamma calls for activation in moderation: lessons from genetics and pharmacology. *Endocrine Reviews* **25**, 899-918.

Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H. and Kangawa, K. (1999) Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* **402**, 656-660.

Kojima, M., Hosoda, H., Matsuo, H. and Kangawa, K. (2001) Ghrelin: discovery of the natural endogenous ligand for the growth hormone secretagogue receptor. *Trends in Endocrinology and Metabolism* **12**, 118-122.

Kolars, J.C., Levitt, M.D., Aouji, M. and Savaiano, D.A. (1984) Yogurt—an autodigesting source of lactose. *New England Journal of Medicine* **310**, 1-3.

Kowalski, T.J., Houpt, T.A., Jahng, J., Okada, N., Chua, S.C. Jr and Smith, G.P. (1998) Ontogeny of neuropeptide Y expression in response to deprivation in lean Zucker rat pups. *American Journal of Physiology* **275**, R466-R470.

Kowalski, T.J., Houpt, T.A., Jahng, J., Okada, N., Liu, S.M., Chua, S.C. Jr and Smith, G.P. (1999) Neuropeptide Y overexpression in the preweanling Zucker (fa/fa) rat. *Physiology and Behavior* **67**, 521-525.

Koylu, E.O., Couceyro, P.R., Lambert, P.D., Ling, N.C., DeSouza, E.B. and Kuhar, M.J. (1997) Immunohistochemical localization of novel CART peptides in rat hypothalamus, pituitary and adrenal gland. *Journal of Neuroendocrinology* **9**, 823-833.

Kristensen, P., Judge, M.., Thim, L., Ribel, U., Christjansen, K.N., Wulff, B.S., Clause, J.T., Jensen, P.B., Madsen, O.D., Vrang, N., Larsen, P.J. and Hastrup, S. (1998) Hypothalamic CART is a new anorectic peptide regulated by leptin. *Nature* **393**, 72-76.

Kubota, N., Terauchi, Y., Miki, H., Tamemoto, H., Yamauchi, T., Komeda, K., Satoh, S., Nakano, R., Ishii, C., Sugiyama, T., Eto, K., Tsubamoto, Y., Okuno, A., Murakami, K., Sekihara, H., Hasegawa, G., Naito, M., Toyoshima, Y., Tanaka, S., Shiota, K., Kitamura, T., Fujita, T., Ezaki, O., Aizawa, S., Nagai, R., Tobe, K., Kimur, S. and Kadowaki, T. (2003) PPAR gamma mediates high-fat diet-induced adipocyte hypertrophy and insulin-resistance. *Molecular Cell* **4**, 597-609.

La Fleur, S.E. (2006) The effects of glucocorticoids on feeding behavior in rats. *Physiology and Behavior In press.*

Laugerette, F., Passilly-Degrace, P., Patris, B., Niot, I., Febbraio, M., Montmayeur, J.P. and Besnard, P. (2005) CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. *Journal of Clinical Investigation* **115**, 3177-3184.

Lee, M.., Somervill, E.M., Kennett, G.A., Dourish, C.T. and Clifton, P.G. (2004) Tonic regulation of satiety by 5-HT receptors

in the mouse: converging evidence from behavioural and c-fos immunoreactivity studies? *European Journal of Neuroscience* **19**, 3017-3025.

Leung, Y.F. and Cavalieri, D. (2003) Fundamentals of cDNA microrray data analysis. *Trends in Genetics* **19**, 649-659.

Levin, B.E. (2001) Glucosensing neurons do more than just sense glucose. *International Journal of Obesity and Related Metabolic Disorders* **25**, S68-S72.

Levin, B.E. (2002) Glucosensing neurons: the metabolic sensors of the brain? *Diabetes, Nutrition and Metabolism* **15**, 274-281.

Lin, M.T., Chu, P.C. and Leu, S.Y. (1983) Effects of TSH, TRH, LH and LHRH on thermoregulation and food and water intake in the rat. *Neuroendocrinology* **37**, 206-211.

Lind, R.W. (1987) Neural connections of the subfornical organ. *In*: GrossP., Ed. Circumventricular organs and body fluids. Boca Raton, FL: CRC Press, pp. 27-42.

Livingstone, D.E., Jones, G.C., Smith, K., Jamieson, P.M., Andrew, R., Kenyon, C.J., and Walker, B.R. (2000) Understanding the role of glucocorticoids in obesity: tissue-specific alterations in corticosterone metabolism in obese Zucker rats. *Endocrinology* **141**, 560-563.

Loftus, T.M., Jaworsky, D.E., Frehywot, G.L., Townsend, C.A., Ronnett, G.V., Lane, M.D. and Kuhajda, F.P. (2000) Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. *Science* **288**, 2379-2381.

Loktionov, A. (2003) Common gene polymorphisms and nutrition: emerging links with pathogenesis of multifactorial chronic diseases. *Journal of Nutritional Biochemistry*. **14**, 426-451 *Erratum in*: *Journal of Nutritional Biochemistry* **15**, 248.

Lowe, M.E., Kaplan, M.H., Jackson-Grusby, L., D'Agostino, D. and Grusby, M.J. (1998) Decreased neonatal dietary fat absorption and T cell cytotoxicity in pancreatic lipase-related protein 2-deficient mice. *Journal of Biological Chemistry* **273**, 31215-31221.

Lowell, B.B. (1999) PPARgamma: an essential regulator of adipogenesis and modulator of fat cell function. *Cell* **99**, 239-242.

Maassen, C.B.M., van Holten-Neelen, C., Blak, F., Heijne den Bak-Glashouwer, J., Leer, R.J., Laman, J.D., Boersma, W.J.A. and Claassen, E. (2000) Strain-dependent induction of cytokine profiles in the gut by orally administrered *Lactobacillus* strains. *Vaccine* **18**, 2613-2623.

Madsen, L., Petersen, R.K. and Kristiansen, K. (2005) Regulation of adipocyte differentiation and function by polyunsaturated fatty acids. *Biochimical and Biophysical Acta* **1740**, 266-286.

Maffei, M., Fei, H., Lee, G.H., Dani, C., Leroy, P., Zhang, Y., Proenca, R., Negrel, R., Ailhaud, G. and Friedman, J.M. (1995) Increased expression in adipocytes of ob RNA in mice with lesions of the hypothalamus and with mutations at the db locus. *Proceedings of the National Academy of Sciences of the United States of America* **92**, 6957-6960.

Majdic, G., Young, M., Gomez-Sanchez, E., Anderson, P., Szczepaniak, L.S., Dobbins, R.L., McGarry, J.D. and Parker, K.L. (2002) Knockout mice lacking steroidogenic factor 1 are a novel genetic model of hypothalamic obesity. *Endocrinology* **143**, 607-614.

Manichanh, C., Rigottier-Gois, L., Bonnaud, E., Gloux, K., Pelletier, E., Frangeul, L., Nalin, R., Jarrin, C., Chardon, P., Marteau, P., Roca, J. and Dore, J. (2006) Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. *Gut* **55**, 205-211.

Massiera, F., Saint-Marc, P., Seydoux, J., Murata, T., Kobayashi, T., Narumiya, S., Guesnet, P., Amri, E.Z., Negrel, R. and Ailhaud, G. (2003) Arachidonic acid and prostacyclin signaling promote adipose tissue development: a human health concern? *Journal of Lipid Research* **44,** 271-279.

Matson, C.A. and Ritter, R.C. (1999) Long-term CCK-leptin synergy suggests a role for CCK in the regulation of body weight. *American Journal of Physiology* **276**, R1038-R1045.

Mayer, J. (1953) Glucostatic mechanism of regulation of food intake. *New England Journal of Medicine* **249**, 13-16.

Mercenier, A., Hols, P., Roussel, Y., Perez-Martinez, G., Buesa, J., Wilks, M., Pozzi, G., Remaut, E., Morelli, L., Grangette, C., Monedero, V., Palumbo, E., Foligne, B., Steidler, L. and Nutten, S. (2004) Screening and construction of probiotic strains with enhanced protective properties against intestinal disorders. *MEDH: Microbial Ecology in Health and Disease* **16**, 86-95.

Miller, W.H., Faust, I.M., and Hirsch, J. (1984) Demonstration of de novo production of adipocytes in adult rats by biochemical and radioautographic techniques. *Journal of Lipid Research* **254**, 336-347.

Milner, J.A. (2000) Functional foods: the US perspective. *American Journal of Clinical Nutrition* **71**, 1654S-9S; discussion 1674S-5S.

Mitchel, J.S. and Keesey, R.E. (1977) Defense of a lowered weight maintenance level by lateral hypothamically lesioned rats: evidence from a restriction-refeeding regimen. *Physiology and Behavior* **18**, 1121-1125.

Mitsuoka, T., Hayakawa, K. and Kimura, N. (1975) [The fecal flora of man. III. Communication: The composition of Lactobacillus flora of different age groups (author's transl)]. *Zentralblatt für Bakteriology [Orig A]* **232**, 499-511.

Monnikes, H., Lauer, G. and Arnold, R. (1997) Peripheral administration of cholecystokinin activates c-fos expression in the locus coeruleus/subcoeruleus nucleus, dorsal vagal complex and paraventricular nucleus via capsaicin-sensitive vagal afferents and CCK-A receptors in the rat. *Brain Research* **770**, 277-288.

Moraes, R.C., Blondet, A., Birkenkamp-Demstroeder, K., Tirard, J., Orntoft, T.F., Gertler, A., Durand, P., Naville, D. and Begeot, M. (2003) Study of the alteration of gene expression in adipose tissue of diet-induced obese mice by microarray and reverse transcription polymerase chain reaction analysis. *Endocrinology* **144**, 477-4782.

Moran, T.H., Baldessarini, A.R., Salorio, C.F., Lowery, T. and Schwartz, G.J. (1997) Vagal afferent and efferent contributions to the inhibition of food intake by cholecystokinin. *American Journal of Physiology* **272**, R1245-R1251.

Moreau, M.C., Ducluzeau, R. and Raibaud, P. (1976) Hydrolysis of urea in the gastrointestinal tract of "monoxenic" rats: effect of immunization with strains of ureolytic bacteria. *Infection and Immunity* **13**, 9-15.

Morgan, K., Obici, S. and Rossetti, L. (2004) Hypothalamic responses to long-chain fatty acids are nutritionally regulated. *Journal of Biological Chemistry* **279,** 31139-31148.

Moro, G., Minoli, I., Mosca, M., Fanaro, S., Jelinek, J., Stahl, B. and Boehm, G. (2002) Dosage-related bifidogenic effects of galacto- and fructooligosaccharides in formula-fed term infants. *Journal of Pediatric Gastroenterology and Nutrition* **34**, 291-295.

Morton, G.J., Niswender, K.D., Rhodes, C.J., Myers, M.G. Jr, Blevins, J.E., Baskin, D.G. and Schwartz, M.W. (2003) Arcuate nucleus-specific leptin receptor gene therapy attenuates the obesity phenotype of Koletsky (fa(k)/fa(k)) rats. *Endocrinology* **44**, 2016-2024.

Moser, S.A. and Savage, D.C. Bile salt hydrolase activity and resistance to toxicity of conjugated bile salt are unrelated properties in lactobacilli. (2001) *Applied and Environmental Microbiology* **67**, 3476-3480.

Mueller, S., Saunier, K., Hanisch, C., Norin, E., Alm, L., Midtvedt, T., Cresci, A., Silvi, S., Orpianesi, C., Verdenelli, M.C., Clavel, T., Koebnick, C., Zunft, H.J., Dore, J. and Blau, M. (2006) Differences in fecal microbiota in different European study populations in relation to age, gender, and country: a cross-sectional study. *Applied and Environmental Microbiology* **72**, 1027-1033.

Münzberg, H., Flier, J.S. and Bjorbaek, C. (2004) Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. *Endocrinology* **145**, 4880-4889.

Myers, E.A. and Rinaman, L. (2002) Viscerosensory activation of noradrenergic inputs to the amygdala in rats. *Physiology and Behavior* **77**, 723-729.

Nadler, S.T., Stoehr, J.P., Schueler, K.L., Tanimoto, G., Yandell, B.S. and Attie, A.D. (2000) The expression of adipogenic genes is decreased in obesity and diabetes mellitus. *Proceedings of the National Academy of Sciences of the United States of America* **97**, 11371-11376.

Nakazato, M., Murakami, N., Date, Y., Kojima, M., Matsuo, H., Kangawa, K. and Matsukura, S. (2001) A role for ghrelin in the central regulation of feeding. *Nature* **409**, 194-198.

Neish, A.S., Gewirtz, A.T., Zeng, H., Young, A.N., Hobert, M.E., Karmali, V., Rao, A.S. and Madara, J.L. (2000) Prokaryotic regulation of epithelial responses by inhibition of IkappaB-alpha ubiquitination. *Science* **289**, 1560-1563.

Nonogaki, K., Strack, A.M., Dallman, M.F. and Tecott, L.H. (1998) Leptin-independent hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT2C receptor gene. *Nature Medicine* **4**, 1152-1156.

Nonogaki, K., Ohashi-Nozue, K. and Oka, Y. (2006) A negative feedback system between brain serotonin systems and plasma active ghrelin levels in mice. *Biochemical and Biophysical Research Communications* **341**, 703-707.

Ntambi, J.M. and Young-Cheul, K. (2000) Adipocyte differentiation and gene expression. *Journal of Nutrition* **130**, 3122S-3126S.

Olney, J.W. (1969) Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. *Science* **164**, 719-721.

Oomura, Y., Ono, T., Ooyama, H. and Wayner, M.J. (1969) Glucose and osmosensitive neurones of the rat hypothalamus. *Nature* **222**, 282-284.

Petrovich, G.D., Holland, P.C. and Gallagher, M. (2005) Amygdalar and prefrontal pathways to the lateral hypothalamus are activated by a learned cue that stimulates eating. *Journal of Neuroscience* **25**, 8295-8302.

Plata-Salaman, C.R. (1995) Cytokines and feeding suppression: an integrative view from neurologic to molecular levels. *Nutrition* **11**, 674-677.

Primeaux, S.D., York, D.A. and Bray, G.A. (2006) Neuropeptide Y administration into the amygdala alters high fat food intake. *Peptides In Press.*

Prodi, E. and Obici, S. (2006) The brain as a molecular target for diabetic therapy. *Endocrinology* **147**, 2664-2669.

Qu, D., Ludwig, D.S., Gammeltoft, S., Piper, M., Pelleymounter, M.A. Cullen, M.., Mathes, W.F., Przypek, R., Kanarek, R. and Maratos-Flier, E. (1996) A role for melanin-concentrating hormone in the central regulation of feeding behaviour. *Nature* **380**, 243-247.

Raclot, T. and Oudart, H. (1999) Selectivity of fatty acids on lipid metabolism and gene expression. *The Proceedings of the Nutrition Society* **58**, 633-646.

Rakoff-Nahoum, S., Paglino, J., Eslami-Varzaneh, F., Edberg, S. and Medzhitov, R. (2004) Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell* **118**, 229-241.

Rangwala, S.M. and Lazar, M. (2000) Transcriptional control of adipogenesis. *Annual Review of Nutrition* **20**, 535-559.

Rask, E., Olsson, T., Soderberg, S., Andrew, R., Livingstone, D.E., Johson, O. and Walker, B.R. (2001) Tissue-specific dysregulation of cortisol metabolism in human obesity. *Journal of Clinical Endocrinology and Metabolism* **86**, 1418-1421.

Rawls, J.F., Samuel, B.S. and Gordon, J.I. (2004) Gnotobiotic zebrafish reveal evolutionarily conserved responses to the gut microbiota. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 4596-4601.

Reitman, M.L., Arioglu, E., Gavrilova, O., Taylor, S.I. (2000) Lipoatrophy revisited. *Trends in Endocrinology and Metabolism* **11**, 410-416.

Ribot, J., Felipe, F., Bonet, M.L. and Palou, A. (2001) Changes of adiposity in response to vitamin A status correlate with changes of PPAR gamma 2 expression. *Obesity Research* **9**, 500-509.

Rinaman, L., Verbalis, J.G., Stricker, E.M. and Hoffman, G.E. (1993) Distribution and neurochemical phenotypes of caudal medullary neurons activated to express cfos following peripheral administration of cholecystokinin. *Journal of Comparative Neurology* **338**, 475-490.

Rinaman, L., Baker, E.A., Hoffman, G.E., Stricker, E.M. and Verbalis, J.G. (1998) Medullary c-Fos activation in rats after ingestion of a satiating meal. *American Journal of Physiology* **275**, R262-R268.

Roberfroid, M.B. (2000) Prebiotics and probiotics: are they functional foods? *American Journal of Clinical Nutrition* **71**, 1682S-7S; discussion 1688S-90S.

Robinson, K., Chamberlain, L.M., Schofield, K.M., Wells, J.M. and Le Page, R.W.F. (1997) Oral vaccination of mice against tetanus with recombinant *Lactococcus lactis*. *Nature Biotechnology* **15**, 653-657.

Rojdmark, S., Calissendorff, J., Danielsson, O. and Brismar, K. (2005) Hunger-satiety signals in patients with Graves' thyrotoxicosis before, during, and after long-term pharmacological treatment. *Endocrine* **27**, 55-61.

Rosen, E.D., Walkey, C.J., Puigserver, P. and Spiegelman, B.M. (2000) Transcriptional control of adipogenesis. *Genes and Development* **14**, 1293-1307.

Rosen, E.D. (2005) The transcriptional basis of adipocyte development. *Prostaglandins Leukotriens and Essential Fatty Acids* **73**, 31-34.

Sakurai, T., Amemiya, A., Ishii, M., Matsuzaki, I., Chemelli, R.M., Tanaka, H., Williams, S.C., Richardso, J.A., Kozlowski, G.P., Wilson, S., Arch, J.R., Buckingham, R.E., Haynes, A.C., Carr, S.A., Annan, R.S., McNulty, D.E., Liu, W.S., Terrett, J.A., Elshourbagy, N.A., Bergsma, D.J. and Yanagisawa, M. (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* **92**, 573-585.

Sampath, H. and Ntambi, J.M. (2005) Polyunsaturated fatty acid regulation of genes of lipid metabolism. *Annual Reviews of Nutrition* **25**, 317-340.

Sanders, M.E., and Huis in't Veld, J. (1999) Bringing a probiotic-containing functional food to the market: microbiological, product, regulatory and labeling issues. *Antonie Van Leeuwenhoek* **76**, 293-315.

Saper, C.B. (1985) Organization of cerebral cortical afferent systems in the rat. II. Hypothalamocortical projections. *Journal of Comparative Neurology* **237**, 21-46.

Saper, C.B., Chou, T.C. and Elmquist, J.K. (2002) The need to feed: homeostatic and hedonic control of eating. *Neuron* **36**, 199-211.

Savage, D.C. (1977) Microbial ecology of the gastrointestinal tract. *Annual Review of Microbiology* **31**, 107-33.

Saxerholt, H., and Midtved, T. (1986) Intestinal deconjugation of bilirubin in germfree and conventional rats. *Scandinavian Journal of Clinical and Laboratory Investigation* **46**, 341-344.

Schaffler, A., Binart, N., Scholmeric, J. and Buchler, C. (2005) Hypothesis paper: Brain talks with fat—evidence for a hypothalamic-pituitary-adipose axis? *Neuropeptides* **39**, 363-367.

Scharrer, E. (1999) Control of food intake by fatty acid oxidation and ketogenesis. *Nutrition* **15**, 704-714.

Schmidt, M.. and Duncan, B.B. (2003) Diabesity: an inflammatory metabolic condition. *Clinical Chemistry and Laboratory Medicine* **41**, 1120-1130.

Scholz-Ahrens, K.E., Schaafsma, G., van den Heuvel, E.G. and Schrezenmeir, J. (2001) Effects of prebiotics on mineral metabolism. *American Journal of Clinical Nutrition* **73**, 459S-464S.

Schwartz, M.W., Seeley, R.J., Woods, S.C., Weigle, D.S., Campfield, L.A., Burn, P. and Baskin, D.G. (1997) Leptin increases hypothalamic pro-opiomelanocortin mRNA expression in the rostral arcuate nucleus. *Diabetes* **46**, 2119-2123.

Schwartz, M.W., Woods, S.C., Porte, D. Jr, Seeley, R.J. and Baskin, D.G. (2000) Central nervous system control of food intake. *Nature* **404**, 661-671.

Serrero, G., Lepak, N.M. and Goodrich, S.P. (1992) Paracrine regulation of adipose differentiation by arachidonate metabolites: prostaglandin-F2-alpha inhibits early and late markers of differentiation in the adipogenic cell line 1246. *Endocrinology* **131**, 2545-2551.

Sheil, B., McCarthy, J., O'Mahony, L., Bennett, M.W., Ryan, P., Fitzgibbon, J.J., Kiely, B., Collins, J.K. and Shanahan, F. (2004) Is the mucosal route of administration essential for probiotic function? Subcutaneous administration is associated with attenuation of murine colitis and arthritis. *Gut* **53**, 694-700.

Shintani, M., Ogawa, Y., Ebihara, K., Aizawa-Abe, M., Miyanaga, F., Takaya, K., Hayashi, T., Inoue, G., Hosoda, K., Kojima, M., Kangawa, K. and Nakao, K. (2001) Ghrelin, an endogenous growth hormone secretagogue, is a novel orexigenic peptide that antagonizes leptin action through the activation of hypothalamic neuropeptide Y/Y1 receptor pathway. *Diabetes* **50**, 227-232.

Smart, J.L., Tolle, V. and Low, M.J. (2006) Glucocorticoids exacerbate obesity and insulin resistance in neuron-specific proopiomelanocortin-deficient mice. *Journal of Clinical Investigation* **116**, 495-505.

Smith, G.P. and Epstein, A.N. (1969) Increased feeding in response to decreased glucose utilization in the rat and monkey. *American Journal of Physiology* **217**, 1083-1087.

Smith, J., Al-Amri, M., Dorairaj, P. and Snideman, A. (2006) The adipocyte life cycle hypothesis. *Clinical Science (London)* **110**, 1-19.

Sobhani, I., Bado, A., Vissuzaine, C., Buyse, M., Kermorgant, S., Laigneau, J.-P ;, Attoub, S., Lehy, T., Henin, D., Mignon, M., and Lewin, M.J. (2000) Leptin secretion and leptin receptor in the human stomach. *Gut* **47**, 178-183.

Soukas, A., Cohen, P., Socci, N.D. and Friedman, J.M. (2000) Leptin-specific patterns of gene expression in white adipose tissue. *Genes and Development* **14**, 963-980.

Stanley, B.G., Daniel, D.R., Chin, A.S. and Leibowitz, S.F. (1985) Paraventricular nucleus injections of peptide YY and neuropeptide Y preferentially enhance carbohydrate ingestion. *Peptides* **6**, 1205-1211.

Stappenbeck, T.S., Hooper, L.V., Manchester, J.K., Wong, M.H. and Gordon, J.I. (2002a) Laser capture microdissection of mouse intestine: characterizing mRNA and protein expression, and profiling intermediary metabolism in specified cell populations. *Methods in Enzymology* **356**, 167-196.

Stappenbeck, T.S., Hooper, V.L. and Gordon, J.I. (2002b) Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. *Proceedings of the National Academy of Sciences of the United States of America* **99**, 15451-15455.

Steidler, L., Hans, W., Schotte, L., Neirynck, S., Obermeier, F., Falk, W., Fiers, W. and Remaut, E. (2000) Treatment of murine colitits by *Lactococcus lactis* secreting interleukin-10. *Science* **289**, 1352-1355.

Strack, A.M., Sebastian, R.J., Schwartz, M.W. and Dallman, M.F. (1995) Glucocorticoids and insulin: reciprocal signals for energy balance. *American Journal of Physiology* **268**, R142-R149.

Suzawa, M., Takada, I., Yanagisawa, J., Ohtake, F., Ogawa, S., Yamauchi, T., Kadowaki, T., Takeuchi, Y., Shibuya, H., Gotoh, Y., Matsumoto, K. and Kato, S. (2003) Cytokines suppress adipogenesis and PPAR-gamma function through the TAKI/TABI/NIK cascade. *Nature Cell Biology* **5**, 224-230.

Takahashi, T., Kushiro, A., Nomoto, K., Uchida, K., Morotomi, M., Yokokura, T. and Akaza, H. (2001) Antitumor effects of the intravesical instillation of heat killed cells of the Lactobacillus casei strain Shirota on the murine orthotopic bladder tumor MBT-2. *Journal of Urology* **166**, 2506-2511.

Taleb, S., Van Haaften, R., Henegar, C., Hukshorn, C., Cancello, R., Pelloux, V., Hanczar, B, Viguerie, N., Langin, D., Evelo, C., Zucker, J., Clement, K. and Saris, W.H. (2006) Microarray profiling of human white adipose tissue after exogenous leptin injection. *European Journal of Clinical Investigation* **36**,153-163.

Tanaka, T., Yoshida, N., Kishimoto, T. and Akira, S. (1997) Defective adipocyte differentiation in mice lacking the C/EBP-beta and/or CEBP-delta gene. *EMBO Journal* **16**, 7432-7443.

Taranto, M.P., Medici, M., Perdigon, G., Ruiz Holado, A.P. and Valdez, G.F. (2000) Effect of *lactobacillus reuteri* on the prevention of hypercholesterolemia in mice. *Journal of Dairy Science* **83**, 401-403.

Tartaglia, L.A., Dembski, M., Weng, X., Deng, N., Culpepper, J., Devo, R., Richards, G.J., Campfield, L.A., Clark, F.T., Deeds, J., Muir, C., Sanker, S., Moriarty, A., Moore, K.J., Smutko, J.S., Mays, G.G., Wool, E.A., Monroe, C.A. and Tepper, R.I. (1995) Identification and expression cloning of a leptin receptor, OB-R. *Cell* **83**, 1263-1271.

Tartaglia, L.A. (1997) The leptin receptor. *Journal of Biological Chemistry* **272**, 6093-6096.

Tecott, L.H., Sun, L.M., Akana, S.F., Strack, A.M., Lowenstein, D.H., Dallman, M.F. and Julius, D. (1995) Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. *Nature* **374**, 542-546.

Tempel, D.L., McEwen, B.S. and Leibowitz, S.F. (1992) Effects of adrenal steroid agonists on food intake and macronutrient

selection. *Physiology and Behavior* **52**, 1161-1166.

Thompson, D.A. and Campbell, R.G. (1977) Hunger in humans induced by 2-deoxy-D-glucose: glucoprivic control of taste preference and food intake. *Science* **198**, 1065-1068.

Thornton, J.E., Cheung, C.C., Clifton, D.K. and Steiner, R.A. (1997) Regulation of hypothalamic proopiomelanocortin mRNA by leptin in ob/ob mice. *Endocrinology* **138**, 5063-5066.

Tong, Q., Dalgin, G., Xu, H., Ting, C.N., Leiden, J.M. and Hotamisligil, G.S. (2000) Function of GATA transcription factors in pre-adipocyte-adipocyte transition. *Science* **290**, 134-138.

Tschop, M., Smiley, D.L. and Heiman, M.L. (2000) Ghrelin induces adiposity in rodents. *Nature* **407**, 908-913.

Viguerie, N., Poitou, C., Cancello, R., Stich, V., Clément, K. and Langin, D. (2005) Transcriptomics applied to obesity and caloric restriction. *Biochimie* **87**, 117-123.

Wabitsch, M., Hauner, H., Heinze, E. and Teller, W.M. (1995) The role of growth hormone/insulin-like growth factors in adipocyte differentiation. *Metabolism* **44**, 45-49.

Wallenius, V., Wallenius, K., Ahren, B., Rudling, M., Carlsten, H., Dickson, S.L., Ohlsson, C. and Jansson, J.-O. (2002) Interleukin-6-deficient mice develop mature-onset obesity. *Nature Medicine* **8**, 75-79.

Wang, X., and Gibson, G.R. (1993) Effects of the in vitro fermentation of oligofructose and inulin by bacteria growing in the human large intestine. *Journal of Applied Bacteriology* **75**, 373-380.

Wang, N.D., Finegold, M.J. and Bradley, A. (1995) Impaired energy homeostasis in C/EBP alpha knockout mice. *Science* **269**, 1108-1112.

Warwick, Z.S. (2003) Dietary fat dose dependently increases spontaneous caloric intake in rat. *Obesity Research* **11**, 859-864.

Weisberg, S.P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R.L. and Ferrante, A.W.Jr. (2003) Obesity is associated with macrophage accumulation in adipose tissue. *Journal of Clinical Investigation* **112**, 1796-1808.

Willesen, M.G., Kristensen, P. and Romer, J. (1999) Co-localization of growth hormone secretagogue receptor and NPY mRNA in the arcuate nucleus of the rat. *Neuroendocrinology* **70**, 306-16.

Willson, T.M., Lambert, M.H. and Kliewer, S.A. (2001) Peroxisome proliferator-activated receptor gamma and metabolic disease. *Annual Review of Biochemistry* **70**, 341-367.

Woods, S.C., Lotter, E.C., McKay, L.D. and Porte, D. Jr. (1979) Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. *Nature* **282**, 503-505.

Wostmann, B.S., Larkin, C., Moriarty, A. and Bruckner-Kardoss, E. (1983) Dietary intake, energy metabolism, and excretory losses of adult male germfree Wistar rats. *Laboratory Animal Science* **33**, 46-50.

Wu, Z., Bucher, N.L. and Farmer, S.R. (1996) Induction of peroxisome proliferator-activated receptor-gamma during the conversion of 3T3 fibroblasts into adipocytes is mediated by C/EBP-beta, C/EBP-delta, and glucocorticoids. *Molecular and Cellular Biology* **64**, 251-260.

Xu, H., Hirosumi, J., Uysal, K.T., Guler, A.D. and Hotamisligil, G.S. (2002) Exclusive action of transmembrane TNF-alpha in adipose tissue leads to reduced adipose mass and local but not systemic insulin-resistance. *Endocrinology* **143**, 1502-1511.

Xu, J., Bjursell, M.K., Himrod, J., Deng, S., Carmichael, L.K., Chiang, H.C., Hooper, L.V. and Gordon, J.I. (2003) A genomic view of the human-Bacteroides thetaiotaomicron symbiosis. *Science* **299**, 2074-2076.

Xu, H., Barnes, G.T., Yang, Q., Tan, G., Yang, D., Chou, C.J., Sole, J., Nichols, A., Ros, J.S., Tartaglia, L.A., and Chen, H. (2003) Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *Journal of Clinical Investigation* **112**, 1821-1830.

Yang, X., Jansson, P.A., Nagaev, I., Jack, M.M., Carvalho, E., Sunnerhagen, K.S., Cam, M.C., Cushman, S.W. and Smith, U. (2004) Evidence of impaired adipogenesis in insulin resistance. *Biochemical and Biophysical Research Communications* **317**, 1045-15051.

Zittel, T.T., Glatzle, J., Kreis, M.E., Starlinger, M., Eichner, M., Raybould, H.E., Becker, H.D. and Jehle, E.C. (1999) C-*fos* protein expression in the nucleus of the solitary tract correlates with cholecystokinin dose injected and food intake in rats. *Brain Research* **846**, 1-11.

Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L. and Friedman, J.M. (1994) Positional cloning of the mouse obese gene and its human homologue. *Nature* **372**, 425-432.

Zhang, J., Fu, M., Cui, T., Xiong, C., Xu, K., Zhong, W., Xiao, Y., Floyd, D., Liang, J., Li, E., Song, O. and Chen, Y.E. (2004) Selective disruption of PPARgamma2 impairs the development of adipose tissue and insulin sensitivity. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 10703-10708.

Zoetendal, E.G., Akkerman, A.D., Akkerman-van Vliet, W.M., de Visser, J. and de Vos, W.M. (2001) The host genotype affects the bacterial community in the human gastrointestinal tract. *Microbial Ecology and Health Diseases* **13,** 129-134.

Zoetendal, E.G., Vaughan, E.E. and de Vos, W.M. (2006) A microbial world within us. *Molecular Microbiology* **59,** 1639-1650.