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NEUROPEPTIDE AND PERIPHERAL HORMONE CROSSTALK WITH ADIPOCYTE FUNCTION

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ABSTRACT: ***In the wake of the expanding obesity epidemic, adipose tissue has become a focus of intense biomedical research. The organ long held to be a simple repository of fat has evolved into a pivotal player which is actively engaged in the regulation of energy homeostasis. To date, three main features of adipose tissue have been identified to be critical for the integrity of multiple physiologic systems, i. e. insulin sensitivity, adrenergic sensitivity including thermogenic capacity, and endocrine activity. The modulation of these functional characteristics may be an integral part of the physiologic actions of multiple hormones and neuropeptides that are involved in the regulation of energy homeostasis. Here, we summarize recent insights into this hormonal and neuroendocrine crosstalk with adipose tissue. The dissection of mechanisms employed by these factors to impact on adipose tissue biology may open new avenues for the treatment of disorders associated with a dysregulated energy homeostasis and its deleterious metabolic and cardiovascular complications.***

KEY WORDS: Adipocyte, Insulin resistance, Metabolic syndrome, Neuropeptide, Peripheral Hormone

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INTRODUCTION

The cloning of the adipocyte-derived hormone leptin in 1994 is considered by many as the watershed discovery that marked a paradigm shift in metabolic research. The long-held assumption that adipose tissue serves as the body's first and foremost, but rather passive, energy storage site has subsequently been abandoned. Today, we have learned that adipose tissue produces a plethora of messengers that are actively engaged in energy control. At the same time, adipose tissue is an important integrator of endocrine and neuronal signals (Frühbeck *et al.*, 2001). Selective defects in adipose tissue physiology have been shown to entail profound consequences for the maintenance of energy and glucose homeostasis and associated complications both in animal and human studies.

Main characteristics of adipocyte function

Adipocytes display three main functional features (Table 1). First, adipocytes are exquisitely sensitive to insulin, a prototypic anabolic hormone. Among the classical responses to insulin are an increase in glucose uptake, lipogenesis, and cellular proliferation and differentiation (Klein *et al.*, 2002). Insulin suppresses catabolic functions such as lipolysis. Second, adipocytes respond to adrenergic stimulation with catabolic reactions including lipolysis and non-shivering thermogenesis, the latter by virtue of the mitochondrial uncoupling protein-1 (UCP 1) which is specifically expressed in brown adipose tissue (BAT) and regulated by β-adrenergic receptors, in particular the β3-adrenergic receptor (Klein *et al.*, 2000). Anabolic functions such as lipogenesis are suppressed by adrenergic stimulation. As indicated by its name, UCP-1 uncouples oxidative phosphorylation from ATP synthesis and, instead, releases the energy stored in the proton gradient across the mitochondrial membrane as heat. Third, the secretion of hormones, so-called adipokines, marks adipose tissue as an endocrine organ (Fasshauer and Paschke, 2003; Kershaw and Flier, 2004). Besides adipokines, adipose tissue releases non-esterified fatty acids (NEFA); the discussion of NEFA and their role in the pathophysiology of insulin resistance and the metabolic syndrome is beyond the scope of this review. A number of in-depth reviews on this subject exist (Boden and Shulman, 2002; Lewis *et al.*, 2002; Bays *et al.*, 2004).

Disturbances of any one of these three key features may effectively alter adipocyte biology and, on a systemic level, whole-body physiology. First, adipose-selective impairment of proximal or distal elements in the insulin-signaling cascade affects insulin sensitivity in muscle and liver, can protect from obesity and even prolong life span (Tozzo *et al.*, 1997; Minokoshi *et al.*, 2003). Second, polymorphisms in the β3-adrenergic receptor and UCP genes in adipocytes have been linked to human obesity (Clement *et al.*, 1995; Fumeron *et al.*, 1996; Oberkofler *et al.*, 1997; Strosberg, 1997; Valve *et al.*, 1998) and insulin resistance (Walston *et al.*, 1995; Widen *et al.*, 1995). Brown fat-mediated thermogenesis may play an important role in the pathophysiology and treatment of disorders of energy metabolism in mouse and man (Digby *et al.*, 1998; Tiraby and Langin, 2003; Yang *et al.*, 2003). Third, dysregulated adipokine secretion by fat cells is observed in a number of conditions such as obesity, lipodystrophy, diabetes, and atherosclerosis (Fasshauer and Paschke, 2003; Garg, 2004; Goldstein and Scalia, 2004; Kershaw and Flier, 2004) and appears to significantly contribute to a wide range of metabolic, immune, and cardiovascular disease states.

Maintenance of energy homeostasis

A major site of adipokine action is the central nervous system (CNS), establishing a fat-brain axis. In the CNS, complex circuitries process incoming signals and control metabolically active organs such as the liver, skeletal muscle, and, again, fat tissue (Spiegelman and Flier, 2001; Horvath *et al.*, 2004). This efferent control relies heavily on the autonomous nervous as well as neuroendo-crine hormone systems. In this context, recent findings have demonstrated the existence of a direct crosstalk between neuropeptides and adipocytes. In addition, several peripheral hormones, previously unknown for their effects on adipocytes, have been recognized to also participate in this interaction. Given the profound systemic impact of selective modulation of adipose tissue function, such a direct crosstalk could be critical in the pathophysiology of disorders caused by a disturbed energy balance. Furthermore, dissection of this interplay may identify molecular targets for the development of new treatment strategies.

In the following, we will summarize the current state of knowledge about adipocyte interactions with key hormones and neuropeptides involved in the regulation of energy balance. The focus will be on factors that have newly been identified to interact with adipocytes. Interactions are reviewed patterned on the triad of adipocyte functions outlined above with separate sections for lipid metabolism/thermogenesis, insulin sensitivity, and endocrine activity. The data gathered so far have been generated in a considerable number of different model systems. Therefore, a consistent picture is often missing, and conclusions must be drawn with great caution at this state of current knowledge. Adding to the complexity, it should be kept in mind that the origin and composition of adipose tissue is complex and has itself become a major focus of research. This may explain some discrepancies observed when comparing *in vivo* studies with results from experiments *in vitro*. At the end of each main section, concluding remarks aim at focussing the reader on major insights and important unexplored issues.

PERIPHERAL HORMONES

Gastrointestinal hormones

(a) Incretins

Due to its therapeutic potential, the incretin system has recently attracted special attention (Drucker, 2003a). Glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP) represent the dominant incretin peptides (Drucker, 2003a). These gastrointestinal hormones stimulate insulin release in response to food intake. They also induce β-cell expansion and exert extrapancreatic effects including inhibition of food intake (GLP-1), changes in energy expenditure (GIP) (Miyawaki *et al.*, 2002), and modulation of gastric emptying (GIP and GLP-1) (Drucker, 2001; Drucker, 2002; Meier *et al.*, 2002; Drucker, 2003a). Incretin mimetics and degradation inhibitors currently represent the most promising therapeutic option for the treatment of diabetes (Drucker, 2003a; Drucker, 2003b). Their use is also associated with significant weight loss in many clinical studies (Drucker, 2003a; Buse *et al.*, 2004). Inhibition of GIP signaling by GIP receptor disruption in mice protects against diet-induced obesity (Miyawaki *et al.*, 2002). Little is known about incretin action on adipocytes.

GIP: GIP receptors are expressed in primary cultures of rat adipocytes (Usdin *et al.*, 1993; Yip *et al.*, 1998) and

Table 1: The three main features of adipocyte biology

Feature	Examples	Systemic relevance of adipose-specific disturbance
1. Insulin sensitivity	Glucose uptake, lipogenesis	Insulin resistance, protection from diet-induced obesity, increased lifespan
2. β-adrenergic sensitivity	Lipolysis, thermogenesis	Obesity
3. Endocrine activity	Secretion of leptin, adiponectin	Obesity, cardiovascular disease

differentiated 3T3-L1 adipocytes (Yip *et al.*, 1998). They belong to the class of G protein-coupled receptors and stimulate cAMP formation (Yip and Wolfe, 2000). In addition, alternative cAMP-dependent and -independent modes of action have been reported in rat adipocytes (Beck and Max, 1988) and in non-adipose cell lines (Kubota *et al.*, 1997; Ehses *et al.*, 2001; Ehses *et al.*, 2002).

Lipid metabolism/thermogenesis: GIP has been reported to increase basal lipogenesis in rat (Oben *et al.*, 1991) and lamb adipose explants (Baba *et al.*, 2000). Consistent with these findings, GIP has been noted to increase insulin-induced lipogenesis in primary cultures of rat adipocytes (Beck and Max, 1983; Beck and Max, 1988) and to boost the activity of lipoprotein lipase in cultured murine preadipocytes (Eckel *et al.*, 1979). Moreover, GIP suppresses β-adrenergically and glucagon-mediated lipolysis in isolated rat adipocytes (Dupre *et al.*, 1976; Hauner *et al.*, 1988). However, GIP alone has also been reported to increase basal lipolysis in primary rat adipocytes (Beck and Max, 1983; Hauner *et al.*, 1988). Furthermore, an inhibition of insulin-induced lipogenesis has been described in lamb adipose explants (Baba *et al.*, 2000). To our knowledge, GIP effects on thermogenic adipocyte function have not been explored to date.

Insulin sensitivity: GIP increases insulin binding and insulin-dependent glucose uptake (Starich *et al.*, 1985; Hauner *et al.*, 1988).

Endocrine activity: To our knowledge, the regulation of adipokine production by GIP has not yet been investigated.

GLP-1: The expression of the GLP-1 receptor in adipocytes has been a matter of debate. Several studies have observed the expression of the pancreatic GLP-1 receptor *in vitro* by receptor-binding studies in human (Merida *et al.*, 1993) and rat adipocytes (Valverde *et al.*, 1993), and by polymerase chain reaction (PCR) assays in 3T3-L1 adipocytes (Egan *et al.*, 1994). However, in rat adipose tissue, others did not find GLP-1 receptors using RNAse protection, *insitu* hybridization, and PCR assays (Bullock *et al.*, 1996). Moreover, an alternative form of the receptor has been proposed (Montrose-Rafizadeh *et al.*, 1997). This alternative form may lower intracellular cAMP levels (Miki *et al.*, 1996), contrary to the conventional form which stimulates formation of this second messenger.

Lipid metabolism/thermogenesis: GLP-1 seems to exert differential, concentration-dependent effects on lipid metabolism in human adipocytes, which may be explained by the existence of different GLP-1-binding receptors. At low concentrations, GLP-1 was found to act synergistically with insulin to increase lipogenesis in human adipocytes, whereas, at higher concentrations, it augmented glucagon-dependent lipolysis (Villanueva-Penacarrillo *et al.*, 2001). One study did not find any effect of GLP-1 on lipolysis in human subcutaneous adipocytes (Bertin *et al.*, 2001). Likewise, reports on the lipolytic or lipogenic activity of GLP-1 in rodent adipocytes have been contradictory, some supporting the notion of increased lipogenesis (Oben *et al.*, 1991; Egan *et al.*, 1994; Perea *et al.*, 1997), and some the opposite (Ruiz-Grande *et al.*, 1992). Thermogenic activity of BAT was found to be lowered by GLP-1 infusion in one clinical study (Flint *et al.*, 2000).

Insulin sensitivity: There is, however, agreement on the insulin-mimetic effect of GLP-1 on glucose metabolism. GLP-1 potently increases insulin-dependent glucose uptake in adipocytes at low concentrations (1 to 15 nmol/l) (Egan *et al.*, 1994; Miki *et al.*, 1996; Perea *et al.*, 1997). It also res-cues the downregulation of glucose transporter-4 (GLUT-4) brought about by prolonged insulin exposure (Wang *et al.*, 1997).

Endocrine activity: Short-term GLP-1 infusion does not seem to alter leptin levels (Drewes *et al.*, 1997; Shalev *et al.*, 1997). To our knowledge, nothing is known about the regulation of other adipokines by GLP-1.

Conclusion: Both incretin hormones, GIP and GLP-1, appear to interact with adipocyte functions. Enhancement of insulin action may be an important direct effect. However, receptor expression and signalling pathways remain an issue of debate, particularly with respect to GLP-1. Regulation of endocrine adipocyte function is currently virtually unexplored. In view of the considerable therapeutic potential of incretins, this may be an important field of future research efforts.

(b) Ghrelin

Originally described as a growth hormone secretagogue (Kojima *et al.*, 2001), ghrelin is secreted by the gastric mucosa and plays a role in the short-term regulation of energy homeostasis, notably the initiation of feeding (Zigman and Elmquist, 2003). The ghrelin receptor occurs in several CNS and peripheral regions (Korbonits *et al.*, 2004) including adipose tissue (Kojima *et al.*, 1999; Choi *et al.*, 2003; Kim *et al.*, 2004), where an atypical form of the receptor has also been assumed (Zhang *et al.*, 2004).

While knockout models of both ghrelin (Sun *et al.*, 2003) and the ghrelin receptor (Sun *et al.*, 2004) have rather normal phenotypes compared to wildtype controls, ghrelin does seem to impact on adipocyte biology.

Lipid metabolism/thermogenesis: Ghrelin activates the mitogen-activated protein kinase pathway *in vitro* (Kim *et al.*, 2004; Zhang *et al.*, 2004), which stimulates cellular proliferation and differentiation in cultured white adipocytes (Choi *et al.*, 2003; Kim *et al.*, 2004; Zhang *et al.*, 2004). This has been confirmed in rats *in vivo* (Thompson *et al.*, 2004). In brown adipocytes, however, ghrelin does not seem to affect adipocyte differentiation (Ott *et al.*, 2002b). Ghrelin suppresses isoproterenol-induced lipolysis (Choi *et al.*, 2003). In brown adipocytes, however, responses to adrenergic stimulation remain unaffected by ghrelin (Ott *et al.*, 2002b). Still, there may be an indirect modulation of UCP-1 by ghrelin, since central administration of ghrelin suppresses brown adipose thermogenic activity in rats (Yasuda *et al.*, 2003).

Insulin sensitivity: Ghrelin augments insulin sensitivity (Kim *et al.*, 2004) in 3T3-L1 adipocytes as measured by glucose transport. In brown adipocytes, consistent with the lack of direct effects on the thermogenic capacity, insulin-induced glucose uptake remains unaffected by ghrelin (Ott *et al.*, 2002b).

Endocrine activity: Ghrelin directly suppresses adiponectin mRNA expression (Ott *et al.*, 2002b). In one study, intraperitoneal injection of ghrelin increased both adiponectin and leptin expression in adipose tissue, but these effects did not reach statistical significance (Asakawa *et al.*, 2003).

Conclusion: Little is known about ghrelin interactions with adipose tissue functions and related signaling mechanisms. Existing studies suggest only small to no effects in response to adrenergic and insulin stimulation with an apparent dichotomy between white and brown adipocytes. Regulation of adipokines remains largely unexplored with a possible direct ghrelin-induced pattern compatible with the induction of a diabetogenic profile.

Cardiac hormones

Natriuretic peptides

The natriuretic peptide (NP) family of hormones is an integral part of the humoral control of the cardiovascular system. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are secreted by cardiac myocytes and act in a manner to decrease vascular tone, increase glomerular filtration rate and renal excretion of sodium, and inhibit the renin-angiotensin-aldosterone system (RAAS) and SNS activity (Levin *et al.*, 1998). Recently, it has been recognized that NPs may have a role in obesity and the metabolic syndrome. Two clinical studies demonstrated that plasma levels of ANP and BNP are negatively correlated with obesity (McCord *et al.*, 2004; Wang *et al.*, 2004), complementing earlier experiments with obese rats that displayed an increase in circulating ANP during a fast (Crandall *et al.*, 1989).

While the focus of research efforts has been on the cardiovascular and renal effects of NPs, the investigation of NPs in adipocytes has yielded rather surprising results (Kalra and Tigas, 2002). NP receptors are expressed in fat more abundantly than in any other tissue (Sarzani *et al.*, 1996; Dessi-Fulgheri *et al.*, 1998). Expression of the NP 'clearance' receptor, NPR-C, in fat is upregulated in obesity and downregulated during weight loss, leading to enhanced bioactivity of ANP and BNP in the lean state (Sarzani *et al.*, 1995; Dessi-Fulgheri *et al.*, 1998).

Lipid metabolism/thermogenesis: The role of adipose NP receptors remained unclear (Okamura *et al.*, 1988; Jeandel *et al.*, 1989) until five years ago when strong lipolytic effects of ANP and BNP in human adipocytes were described (Sengenès *et al.*, 2000). Apparently, the expression pattern of NP receptors varies between species (Sengenès *et al.*, 2002), explaining why no such effect had been observed in rodents. In primates, including humans, NPs activate a novel lipolytic pathway (Moro *et al.*, 2004b). This may play a physiological role in lipid mobilization in humans (Moro *et al.*, 2004a). In brown adipocytes exposed to BNP, UCP-1 mRNA and protein expression remains unaltered (Christiansen *et al.*, 2005).

Insulin sensitivity: ANP increases oxidative glucose metabolism in cultured rat adipocytes (Crilley and Garcia, 1997), while insulin-induced glucose uptake is unchanged (Christiansen *et al.*, 2005).

Endocrine activity: NPs modulate adipokine expression and secretion. In human adipocytes, ANP inhibits leptin secretion (Fain *et al.*, 2003). In apparent contrast to this, in murine brown adipocytes, BNP stimulation acutely and transiently increases leptin mRNA expression. Furthermore, expression of monocyte chemoattractant protein -1 (MCP-1) and angiotensin II is stimulated by BNP whereas adiponectin levels remain unchanged (Christiansen *et al.*, 2005).

Conclusion: Adipose tissue is a target for natriuretic peptide action. ANP-induced lipolysis is the predominant effect reported to date. However, insulin sensitivity and adipokine expression and secretion appear to be modulated as well. Given the high number of NP receptors on adipocytes as well as the inverse correlation between NP blood levels and obesity, NP-adipocyte crosstalk merits further investigations with regard to metabolic and endocrine interactions.

Renin-angiotensin-aldosterone system (RAAS)

(a) Angiotensin

Angiotensin II (AII) is a strong vasoconstrictive agent. It may link cardiovascular disease to insulin resistance, as angiotensin receptor-1 (AT1) antagonists prevent the onset of diabetes in hypertensive patients (Dahlof *et al.*, 2002; Cooper, 2004). Furthermore, AII seems to have a role in the regulation of body weight, as it promotes weight loss when infused into the cerebrospinal fluid in rats (Porter *et al.*, 2003; Porter and Potratz, 2004).

The AII precursor, angiotensinogen, is expressed in adipose tissue (Engeli *et al.*, 2003). Its mRNA levels in visceral fat are positively correlated with body mass (Giacchetti *et al.*, 2000). Furthermore, angiotensin receptors are expressed in human, rat, and possibly mouse adipocytes (Engeli *et al.*, 2003), defining adipose tissue as a direct target for AII.

Lipid metabolism/thermogenesis: AII may stimulate adipocyte proliferation and differentiation in rodents and mammals (Ailhaud *et al.*, 2000). However, in human fat, the opposite has also been observed (Janke *et al.*, 2002). Angiotensin receptor blockers might inhibit the impairment of adipose tissue formation by AII, thus preventing diabetes by enabling the proper storage of fatty acids (Sharma *et al.*, 2002).

Lipogenesis is increased by AII in both 3T3-L1 and cultured human adipocytes (Jones *et al.*, 1997). With regard to lipolysis however, data remain controversial indicat-

ing an inhibition (Boschmann *et al.*, 2001), no change (Boschmann *et al.*, 2002), or a stimulation (Boschmann *et al.*, 2003) by AII exposure.

Thermogenesis in BAT appears to be regulated by AII in an indirect manner. Following intracerebroventricular administration of AII, UCP-1 expression in BAT is increased, presumably mediated by the sympathetic nervous system (Porter *et al.*, 2003; Porter and Potratz, 2004). In addition, SNS activity in brown fat is locally modulated by AII, which increases norepinephrine release from sympathetic nerve fibers (Cassis and Dwoskin, 1991; Cassis, 1993; Cassis, 1994).

Insulin sensitivity: In cultured 3T3-L1 adipocytes, AII does not affect basal glucose uptake (Wu-Wong *et al.*, 1999). However, the AT1 antagonist telmisartan increases both basal and insulin-dependent glucose uptake in the same cell model (Fujimoto *et al.*, 2004). In cultured human adipocytes, AII does not alter insulin-dependent glucose uptake (Perry *et al.*, 2003). In rats, AII decreases insulin-dependent glucose uptake when administered chronically (Ogihara *et al.*, 2002), whereas the AT1 antagonist losartan has no effect on insulin action (Caldiz and de Cingolani, 1999).

Endocrine activity: On the endocrine level, leptin secretion is directly stimulated by AII in rat (Cassis *et al.*, 2004), mouse, and human adipocytes (Kim *et al.*, 2002). It is unknown whether AII also regulates adiponectin production; however, the AT1 antagonist, telmisartan, stimulates adiponectin mRNA expression in 3T3-L1 adipocytes (Fujimoto *et al.*, 2004). AII and its metabolites increase production of the prothrombotic enzyme, plasminogen-activator inhibitor-1 (PAI 1) in cultured human fat cells (Skurk *et al.*, 2001a; Skurk *et al.*, 2001b). Furthermore, AII stimulates the secretion of the proinflammatory cytokines, interleukin-6 and interleukin-8, in human adipocytes (Skurk *et al.*, 2004).

Conclusion: Although not yet fully understood, AII action on adipose tissue appears to have two important consequences: modulation of adipocyte proliferation/differentiation as well as endocrine function with induction of proinflammatory adipokines. While AII does not affect insulin sensitiv-ity of fat cells directly, it has differential effects on lipid metablism and adrenergic responsiveness. In white adipocytes, it promotes lipogenesis, whereas it enhances uncoupling protein expression in mice.

(b) Aldosterone

The hormonal regulation of salt-water balance and blood pressure relies heavily on the renin-angiotensin-aldosterone system (RAAS). Aldosterone is the classic minerolocorticoid hormone that increases the absorption of sodium and the excretion of potassium in the renal tubules. Aldosterone levels have been linked to obesity (Goodfriend *et al.*, 1998), insulin resistance (Corry and Tuck, 2003), and the metabolic syndrome (Sharma *et al.*, 2001; Aneja *et al.*, 2004). Patients suffering car-diovascular complications of this syndrome benefit from aldosterone receptor antagonists (Pitt *et al.*, 1999; Goossens *et al.*, 2003; Pitt *et al.*, 2003).

Adipose tissue produces all components of the RAAS (Engeli *et al.*, 2003; Aneja *et al.*, 2004) and an as yet unidentified, novel aldosterone secretagogue (Ehrhart-Bornstein *et al.*, 2003). Furthermore, it is a direct target of aldosterone as the mineralocorticoid receptor is endogenously expressed in adipocytes (Le Menuet *et al.*, 2004).

Lipid metabolism/thermogenesis: Aldosterone stimulates adipocyte differentiation (Rondinone *et al.*, 1993; Penfornis *et al.*, 2000). In line with this observation, hyperaldosteronism is associated with enlarged BAT depots (Garruti and Ricquier, 1992) and has been linked to obesity (Goodfriend *et al.*, 1998). An aldosterone-induced decrease in energy expenditure may be postulated, given that this mineralocorticoid hormone interferes with adrenergic effects by inhibiting UCP-1 expression (Viengchareun *et al.*, 2002; Jaeger *et al.*, 2003).

Insulin sensitivity: Insulin-dependent glucose uptake appears to be impaired by aldosterone (Jaeger *et al.*, 2003). Hyperaldosteronism is associated with insulin resistance (Corry and Tuck, 2003).

Endocrine activity: Direct aldosterone action on adipocytes induces alterations in adipokine expression, increasing expression of proinflammatory hormones such as leptin and monocyte chemoattractant protein-1 (MCP-1) (Jaeger *et al.*, 2003). MCP-1 has been associated with insulin resistance and the metabolic syndrome (Sartipy and Loskutoff, 2003). Clinical studies suggest a negative correlation of aldosterone with serum leptin (Torpy *et al.*, 1999; Haluzik *et al.*, 2002).

Conclusion: Adipose tissue is a target for aldosterone action. All key features of adipocyte function appear to be modulated. Alterations mirror the development of core components of the metabolic syndrome including impaired energy expenditure, insulin resistance, and the induction of a proinflammatory profile of adipokine expression. In light of the eminent role of aldosterone for cardiovascular and general stress reactions, this mineralocorticoid-adipocyte interplay may have important implications.

Adipokines – autocrine/paracrine actions

Of all adipokines identified to date, leptin is by far the most extensively studied. It is a pivotal regulator in physiology. Adiponectin, in turn, is one of the most recently identified adipokines with a significant therapeutic potential (Bays, 2004; Havel, 2004). For the purposes of this review, we will focus on these two adipose tissue hormones.

(a) Leptin

Leptin can be considered the prototypic hormone secreted by adipocytes. This peptide, almost exclusively expressed in adipose tissue, has turned out to be of paramount importance for the con-trol of food intake, energy expenditure, and endocrine as well as reproductive functions. The com-

mon forms of human obesity are characterized by high leptin levels and leptin resistance, and administration of leptin does not reduce body weight under these circumstances (Westerterp-Plantenga *et al.*, 2001; Hukshorn *et al.*, 2002). However, recent reports have demonstrated this peptide's therapeutic potential for diseases such as lipodystrophy (Oral *et al.*, 2002; Ebihara *et al.*, 2004) and hypothalamic amenorrhea (Welt *et al.*, 2004).

The leptin receptor (ObR) occurs in five splice variants, ObRa through ObRe (Tartaglia, 1997). The long form, ObRb, mediates leptin's effects (Zabeau *et al.*, 2003); however, ObRa has also been noted to convey signaling (Murakami *et al.*, 1997). By virtue of these receptors, leptin targets almost every peripheral organ system, including the hematopoietic, immune, gastrointestinal, genitourinary, and musculoskeletal systems (Margetic *et al.*, 2002). Both ObRb and ObRa are also present on rodent (Ghilardi *et al.*, 1996; Siegrist-Kaiser *et al.*, 1997) and human (Bornstein *et al.*, 2000) adipocytes.

Lipid metabolism: Leptin induces lipolysis in rodent adipocytes *in vivo* (Frühbeck *et al.*, 1998) and *in vitro* (Wang *et al.*, 1999b; Martinez *et al.*, 2000; Ramsay, 2001; Frühbeck and Gomez-Ambrosi, 2002; Rodriguez *et al.*, 2003). Leptin also decreases lipogenesis in rodents as reflected by reduced fatty acid synthase expression (Wang *et al.*, 1999b). Similarly, porcine adipocytes react with increased lipolysis and decreased lipogenesis to leptin stimulation *in vivo* and *in vitro* (Ajuwon *et al.*, 2003; Ramsay, 2003). In one study that examined leptin effects in sheep, the adipokine did not elicit any effects on lipid metabolism; neither did it stimulate the known leptin messengers STAT3 and STAT5 (Newby *et al.*, 2001). Of note, in cultured human adipocytes leptin has no effect on basal and adrenergically induced lipolysis (Aprath-Husmann *et al.*, 2001; Elimam *et al.*, 2002).

Thermogenesis: Peripheral leptin infusion increases UCP-1 content of brown adipocytes in normal rats (Scarpace *et al.*, 1997; Scarpace *et al.*, 1998; Rouru *et al.*, 1999) and mice (Arvaniti *et al.*, 1998; Commins *et al.*, 1999) and restores the decreased UCP-1 levels seen in *ob/ob* mice (Commins *et al.*, 1999). However, some groups could not reproduce these results (Gomez-Ambrosi *et al.*, 1999) or reproduced them only in fasted animals (Gomez-Ambrosi *et al.*, 1999; Sivitz *et al.*, 1999). Besides UCP-1, UCP-2 and UCP-3 in brown and white adipose tissue appear to be stimulated by leptin as well (Scarpace *et al.*, 1997; Scarpace and Matheny, 1998; Rouru *et al.*, 1999; Sivitz *et al.*, 1999; Scarpace *et al.*, 2000). The changes in uncoupling protein seen under leptin treatment *in vivo* can also be mediated by the sympathetic nervous system. Accordingly, they can be elicited by intracerebroventricular administration (Cusin *et al.*, 1998). Leptin stimulates sympathetic nervous system outflow to BAT (Hausberg *et al.*, 2002; Haynes *et al.*, 2002). Interestingly, the leptin-induced increase of UCP-2 (Scarpace *et al.*, 2000) – but not UCP-1 (Scarpace and Matheny, 1998) – is conserved after BAT denervation.

Insulin sensitivity: Leptin induces insulin resistance *in vitro* in human white (Zhang *et al.*, 1999), rat white (Müller *et al.*, 1997) and murine brown (Kraus *et al.*, 2002) fat cells. Of note, some investigators could not confirm these findings (Mick *et al.*, 1998; Ranganathan *et al.*, 1998; Zierath *et al.*, 1998). *In vivo*, however, peripheral leptin infusion causes insulin resistance only in white adipocytes, while insulin sensitivity was actually increased in brown fat (Siegrist-Kaiser *et al.*, 1997; Wang *et al.*, 1999a). The induction of insulin resistance in adipose tissue seemingly contradicts the overall effect of leptin to increase systemic insulin sensitivity (Pelleymounter *et al.*, 1995; Kamohara *et al.*, 1997). Yet, adipose-selective impairment of insulin signaling, particularly at a very proximal level, protects from diet-induced obesity (Blüher *et al.*, 2003) and improves longevity (Blüher *et al.*, 2003), indicating that tissue-specific alterations can have substantially different effects for the organism on the whole. In this context, it is noteworthy that leptin inhibits insulin receptor kinase activity (Kraus *et al.*, 2002) in a murine adipocyte model. Consistent with this finding, decreased insulin receptor autophosphorylation has been reported in primary rat adipocytes (Perez *et al.*, 2004).

Endocrine activity: The regulation of adipokines by leptin is poorly studied. In mice, chronic infusion of leptin reportedly increases adiponectin mRNA expression and serum levels in white adipose tissue (WAT) but not BAT (Delporte *et al.*, 2004). The same study also found a direct transient, leptin-dependent increase of adiponectin mRNA in cultured 3T3-F442A cells. Concordantly, adipose-specific deletion of leptin receptors in mice decreases adiponectin expression (Huan *et al.*, 2003). On the other hand, adiponectin serum levels are depressed following transgenic expression of leptin in the hypothalamus as well as after peripheral leptin injection (Ueno *et al.*, 2004). In men, neither physiological nor pharmacological doses of leptin affect adiponectin serum levels (Gavrila *et al.*, 2004).

Conclusion: Leptin potently changes metabolic adipose function in an autocrine manner. It fuels UCP-1 expression and induces insulin resistance. An autocrine regulation of endocrine adipocyte function remains enigmatic.

(b) Adiponectin

Adiponectin levels are negatively correlated with obesity and insulin resistance (Kershaw and Flier, 2004) and may predict the onset of diabetes (Spranger *et al.*, 2003). In mouse models both for lipodystrophy and obesity, adiponectin reverses insulin resistance (Yamauchi *et al.*, 2001). Furthermore, this adipokine also normalizes lipid abnormalities and causes weight loss in mice with diet-induced insulin resistance (Fruebis *et al.*, 2001; Maeda *et al.*, 2002). A recent study demonstrated that adiponectin also acts in the brain: Intracerebroventricular administration of adiponectin increased energy expenditure and reduced weight as well as glucose and lipid levels without affecting food

intake (Qi *et al.*, 2004). Two adiponectin receptors subtypes, AdipoR1 and AdipoR2, are expressed in 3T3-L1 adipocytes (Fasshauer *et al.*, 2004). Adiponectin exposure of bone marrow-derived brown adipocytes induces an impairment of cell proliferation and differentiation (Yokota *et al.*, 2002). The globular form of adiponectin increases basal and insulin-dependent glucose uptake in primary rat adipocytes (Wu *et al.*, 2003).

Conclusion: To date, surprisingly little is known about adiponectin interactions with adipocyte biology. In particular, more research is needed to clearly define autocrine adiponectin actions.

NEUROPEPTIDES

Apart from hormones of primarily peripheral origin, nervous system-derived peptides act on adipose tissue in an endocrine or paracrine manner. Some of these neuropeptides are also expressed in peripheral tissues. There are two main groups of neuropeptides that influence the central nervous system control of energy homeostasis, one with orexigenic, i.e. appetite-promoting, and one with anorexigenic properties. The latter comprises the melanocortins α melanocyte-stimulating hormone (α MSH) and adrenocorticotropic hormone (ACTH), cocaine- and amphetamine-regulated transcript (CART), and ciliary neurotrophic factor (CNTF), all of which are stimulated by leptin. The former group of peptides includes orexins, neuropeptide Y, the melanocortin receptor antagonist agouti-related protein (AgRP), melanin-concentrating hormone (MCH), and endocannabinoids. Conversely, the expression of these substances is suppressed by leptin.

(a) Melanocortins

The melanocortin system consists of peptides derived from proopiomelanocortin (POMC) on the one hand, and their respective G-protein coupled receptors (MC1R through MC5R) on the other. α-MSH and ACTH are examples for endogenous agonists, and agouti (in rodents), agouti-signaling-protein (ASP, in humans) and AgRP (in rodents and humans) are endogenous antagonists at melanocortin receptors (Wikberg, 1999; Dinulescu and Cone, 2000). The melanocortin system is critical for the maintenance of energy homeostasis. POMC or melanocortin receptor knockout mice develop components of the metabolic syndrome, as do mice that overexpress the endogenous antagonists (Cummings and Schwartz, 2000; Ellacott and Cone, 2004). In humans, the frequency of MC4R polymorphisms in obesity is approximately 4 %. Melanocortin-derived substances are being investigated for their therapeutic potential (Bays, 2004).

Apart from ACTH, which is secreted into the bloodstream by the anterior pituitary, the neuropeptides α-MSH and AgRP are also released into the circulation. Serum AgRP is correlated to body mass in humans (Katsuki *et al.*, 2001; Gavrila *et al.*, 2004; Hoggard *et al.*, 2004b), but reports on a similar relationship between serum α-MSH and body mass are ambiguous (Katsuki *et al.*, 2000; Nam *et al.*, 2001; Gavrila *et al.*, 2004; Hoggard *et al.*, 2004b). Accumulating evidence indicates that fat tissue is a major site of peripheral melanocortin production and action. For example, the predominant source of the human agouti homolog ASP is the adipocyte (Kwon *et al.*, 1994).

With regard to melanocortin action, fat cells have been shown to bear functional receptors. In cultured mouse adipocytes, MC2R (Grunfeld *et al.*, 1985; Boston and Cone, 1996; Kiwaki and Levine, 2003; Noon *et al.*, 2004) and MC5R (Boston and Cone, 1996) have been described in the 3T3-L1 line, and MC1R, MC2R, and MC5R in the 3T3F-442A line (Mountjoy and Wong, 1997). In primary cultures of rat adipocytes, ACTH-selective MC2R (Oelofsen and Ramachandran, 1983) and MC4R (Hoggard *et al.*, 2004a) have been reported. Human adipocytes appear to contain mRNA for MC1R through MC5R (Chagnon *et al.*, 1997); however, others have questioned the presence of melanocortin receptors other than MC5R in human fat cells (Chhajlani, 1996; Kiwaki and Levine, 2003).

Lipid metabolism/thermogenesis: ACTH and α-MSH are well known to stimulate lipolysis in various species and adipose cell lines (Kastin *et al.*, 1975; Rudman, 1975; Ramachandran *et al.*, 1976; Ramachandran and Lee, 1976; Matsuoka *et al.*, 1978; Richter and Schwandt, 1985; Chernick *et al.*, 1986; Bousquet-Melou *et al.*, 1995; Boston, 1999), including brown adipocytes (Sugihara *et al.*, 1983), but apparently not in humans (Bousquet-Melou *et al.*, 1995; Kiwaki and Levine, 2003). An inhibition of melanocortin-induced lipolysis by insulin has been reported (Solomon *et al.*, 1970; Morimoto *et al.*, 1998).

One intriguing finding is the increase of UCP-1 mRNA and protein following ACTH stimulation in murine brown adipocytes (unpublished data). *In vivo*, ACTH administration induces thermogenesis in chow-fed, but not cafeteria-fed rats (Rothwell and Stock, 1985b). However, Rothwell *et al.* also reported that ACTH repletion partially reversed the increased thermogenic activity of BAT caused by hypophysectomy (Rothwell and Stock, 1985a). In one study, α-MSH restored the defective cold-induced thermoregulation of *ob/ob* mice without showing thermogenic potential in ambient temperature (Forbes *et al.*, 2001). This thermoregulatory property of α-MSH has been postulated to be centrally mediated (Forbes *et al.*, 2001). In this context, stimulation of melanocortin receptors in the brainstem increases UCP-1 expression in brown adipocytes (Williams *et al.*, 2003). However, analogous to the data on ACTH, it is conceivable that α-MSH also has direct effects on UCP-1 in brown adipocytes.

Insulin sensitivity: The interplay of melanocortin action with insulin sensitivity of adipocytes is essentially unknown. In rat adipocytes, ACTH decreases insulin-induced glucose transport in the absence of adenosine (Kuroda *et al.*, 1987), and stimulates glucose uptake in the absence of insulin (Marette and Bukowiecki, 1990; Shirakura *et al.*, 1990). The effects of other melanocortins remain to be explored.

Endocrine activity: Given the fact that adipose-derived substances, notably leptin, regulate melanocortin production in the brain, the existence of melanocortin effects on the endocrine adipose function would close a feedback loop. This is indeed the case. Stimulation with α-MSH for 24 hours decreases leptin expression and secretion in cultured rat adipocytes (Hoggard *et al.*, 2004a). Leptin secretion is rescued by the addition of agouti (Hoggard *et al.*, 2004a), which is an antagonist predominantly on the MC1 and MC4 receptors (Dinulescu and Cone, 2000). In another study using 3T3-L1 adipocytes, a transient inhibition of leptin expression and secretion by α-MSH and ACTH was observed (Norman *et al.*, 2003). In contrast to the melanocortin agonists, agouti increases leptin expression and secretion in 3T3-L1 adipocytes, and this effect is independent of MC4R (Claycombe *et al.*, 2000). Adipose-specific transgenic expression of agouti in mice increases leptin production (Mynatt *et al.*, 1997; Claycombe *et al.*, 2000), but this effect may be due to increased fat mass in the transgenic animals. Little is known to date about melanocortin effects on the expression or secretion of other adipokines. Adiponectin mRNA in WAT from lean or obese mice as well as serum adiponectin levels are not altered by acute or chronic administration of the non-specific melanocortin receptor agonist, melanotan-II (MT-II) (Blüher *et al.*, 2004b).

Conclusion: The melanocortin system is a critical component of energy homeostasis. Adipose tissue appears to contribute substantially to its function by regulating melanocortin production on one hand and by responding to melanocortins on the other. The overall effect of melanocortin receptor agonists appears to be of a catabolic nature. Melanocortins induce lipolysis and increase energy expenditure by means of UCP-1 expression. Adipokine regulation by the melanocortin system is largely unexplored to date.

(b) Cocaine- and amphetamine-regulated transcript

Cocaine- and amphetamine-regulated transcript (CART) is co-localized with POMC in hypothalamic neurons (Wilding, 2002). Compared to melanocortins, its role in feeding and the regulation of body weight appears less pronounced. Still, CART haplodeficiency in mice leads to in-creased body weight under the influence of a high fat diet (Asnicar *et al.*, 2001). Studies investigating the effects of centrally administered CART have produced conflicting results (Dominguez *et al.*, 2004), possibly due to different active forms of CART (Hunter *et al.*, 2004).

Even though originally described as a neuropeptide, CART is also produced in a number of tissues outside the CNS and circulates in the bloodstream (Koylu *et al.*, 1997; Jensen *et al.*, 1999; Murphy *et al.*, 2000; Dominguez *et al.*, 2004).

Thermogenesis: CART directly stimulates UCP-1 mRNA and protein expression (Perwitz *et al.*, 2005). This may complement indirect, centrally mediated actions. Thus, it has been reported that injection of CART into the paraventricular nucleus leads to an increase of several UCP variants in white and brown adipose tissue (Wang *et al.*, 2000), and overexpression of CART in the arcuate nucleus augments UCP-1 mRNA expression (Kong *et al.*, 2003).

Insulin sensitivity: Consistent with an increase in thermogenesis, direct CART actions enhance insulin-induced glucose uptake and increase insulin signaling in brown adipocytes (Perwitz *et al.*, 2005).

Endocrine activity: CART alters leptin expression directly (Perwitz *et al.*, 2005) as well as indirectly via the CNS (Rohner-Jeanrenaud *et al.*, 2002).

Conclusion: Similarly to melanocortins, the catabolic neuropeptide CART induces a negative energy balance by direct and indirect actions on adipose tissue. The modulation of endocrine adipocyte functions remains largely unknown except for an apparent negative effect on leptin.

(c) Ciliary neurotrophic factor

Ciliary neurotrophic factor (CNTF) is expressed in the central and peripheral nervous systems. It acts on leptin-like pathways to promote satiety. A modified form of this peptide is currently being tested in phase III clinical trials for the treatment of obesity (Bays, 2004). In the periphery, the α-subunit of the CNTF receptor, CNTFRα, is expressed in skeletal muscle and other non-adipose organs (Sleeman *et al.*, 2000). Remarkably, in the obese state CNTFRα also emerges in adipose tissue (Zvonic *et al.*, 2003).

Thermogenesis: Thermogenesis, as reflected by β-adrenergically mediated UCP-1 production in brown adipocytes, is increased by CNTF, supporting the general catabolic role of this neuropeptide by direct stimulation (Ott *et al.*, 2002a) and *in vivo* (Blüher *et al.*, 2004a).

Insulin sensitivity: Insulin sensitivity of adipose tissue appears to be unaffected by CNTF (Ott *et al.*, 2002a; Zvonic *et al.*, 2003).

Endocrine activity: CNTF diminishes expression and secretion of leptin (Ott *et al.*, 2004). Given the disproportionately high levels of leptin that implicate leptin resistance in obese people, lowering these levels may serve to restore leptin sensitivity (Scarpace *et al.*, 2002; Ott *et al.*, 2004). In contrast to these data, explants of retroperitoneal fat and serum samples of mice did not exhibit altered leptin content following interperitoneal administration of CNTF five hours earlier (Sarraf *et al.*, 1997).

Conclusion: Little is known about effects on adipose tissue of the anorexigenic CNTF which is soon to be expected on the market as an anti-obesity drug. Existing data point to direct thermogenic actions. Data on the alteration of endocrine adipocyte function are scarce.

(d) Orexins

Orexins are potent stimulators of food intake and regulators of alertness (Williams *et al.*, 2004). They are predominantly expressed in the hypothalamus, but also occur in other areas of the CNS and in the intestinal

nervous system. Of the two known isoforms, orexin A (OXA) and orexin B (OXB), the former appears to play the more prominent role in the regulation of food intake. Both orexins bind to two G protein-coupled receptors, OX_1 and OX_2, with OXA having greater affinity for OX_1 than for OX_2. Of note, these receptors are expressed in the human adrenals, suggesting a role of orexins in the HPA axis (Jöhren *et al.*, 2004). An OX_1 antagonist, SB-334867, has been developed as an anti-obesity agent and shows promising results in animal studies (Haynes *et al.*, 2000; Ishii *et al.*, 2005).

Orexins circulate in the blood stream (Arihara *et al.*, 2001). BAT contains orexin receptor mRNA (Haynes *et al.*, 2002). However, very little is known about the effects of orexins on adipose tissue biology. Intriguingly though, SB-334867 appears to decrease BAT weight while, at the same time, augmenting its typical brownish phenotype and stimulating UCP-1 mRNA (Haynes *et al.*, 2002). These effects were postulated to be mediated by the sympathetic nervous system. But it is important to note that BAT of SB-334867-treated rats expressed OX1 mRNA to a greater extent than BAT of vehicle-treated animals, thus suggesting that circulating orexins directly act on adipose tissue. Furthermore, there is evidence from an *in vivo* study that subcutaneous application of orexin A regulates leptin secretion (Switonska *et al.*, 2002).

Conclusion: Orexin interaction with white and brown adipocyte function remains almost entirely unknown. As this neuropeptide is being studied as a potential anti-obesity agent, orexin-adipocyte interactions may merit further attention.

(e) Melanin-concentrating hormone

Melanin-concentrating hormone (MCH) is an essential orexigenic agent. Experimental deletion of the MCH precursor gene (Shimada *et al.*, 1998) as well as deletion of the MCHR1 gene (Marsh *et al.*, 2002) both lead to reduced body weight. MCH binds two G protein-coupled receptors, MCHR1 and MCHR2 (Shi, 2004). A pharmacological MCHR1 antagonist, SNAP-7941, decreases food intake in rats (Borowsky *et al.*, 2002) and may have the potential to be used in humans (Doggrell, 2003).

Like many of the other neuropeptides, MCH circulates in the blood (Bradley *et al.*, 2000; Stricker-Krongrad *et al.*, 2001). Both MCHR1 (Bradley *et al.*, 2000; Bradley *et al.*, 2002) and MCHR2 (An *et al.*, 2001; Hill *et al.*, 2001) are present on adipocytes (though the latter not on rodent cells (Pissios and Maratos-Flier, 2003)).

Thermogenesis: MCH indirectly suppresses brown adipose UCP-1 by virtue of the sympathetic nervous system (Oldfield *et al.*, 2002; Ito *et al.*, 2003; Pereira-da-Silva *et al.*, 2003).

Insulin sensitivity: Major insulin signaling elements are activated by direct MCH stimulation in 3T3-L1 adipocytes (Bradley *et al.*, 2002).

Endocrine activity: Leptin mRNA expression and protein secretion are directly stimulated by MCH in rat adipocytes (Bradley *et al.*, 2000; Bradley *et al.*, 2001), as are signaling pathways involved in the regulation of leptin in 3T3-L1 adipocytes (Bradley *et al.*, 2002). Leptin, in turn, lowers CNS expression of both MCH (Tritos *et al.*, 2001) and MCHR1 (Kokkotou *et al.*, 2001), thus closing a peripheral-central negative feedback loop.

Conclusion: Adipose tissue endocrine function is modulated by MCH. Reports have focused on leptin expression and secretion so far. Other adipocyte functions have not been investigated.

(f) The endocannabinoid system

A cannabinoid drug, marijuana, is said to have impressive psychotropic (Ashton, 2001) and pain-relieving properties (Baker *et al.*, 2003). The fact that this drug, as well as other cannabinoids, also stimulates appetite and increases weight has long been considered a side effect and has been neglected by the scientific community. For example, when cannabinoid receptor-1 (CB-1) knock-out mice were first generated by two independent groups in 1999, alterations of food intake and energy metabolism were not systematically investigated (Ledent *et al.*, 1999; Zimmer *et al.*, 1999). Zimmer *et al.* merely noted that their knockout mice had normal body weight and temperature (Zimmer *et al.*, 1999). However, two years later, Di Marzo *et al.* thoroughly characterized the effects of cannabinoids on feeding and body weight in the CB-1 knockout model (Di Marzo *et al.*, 2000). Today, the first cannabinoid antagonist aimed at treating obesity, rimonabant, is about to be introduced to the market (Bays, 2004; Korner and Aronne, 2004).

Cannabinoid receptors have been described in numerous peripheral organs, including the immune (Klein *et al.*, 2003), genitourinary (Das *et al.*, 1995; Pertwee and Fernando, 1996), respiratory (Rice *et al.*, 1997), cardiovascular (Batkai *et al.*, 2004), and gastrointestinal systems (Croci *et al.*, 1998; Massa *et al.*, 2004). Interestingly, there is a differentiation-dependent expression of CB-1 in adipocytes, which is further augmented in the obese state (Bensaid *et al.*, 2003; Cota *et al.*, 2003).

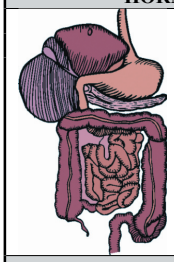
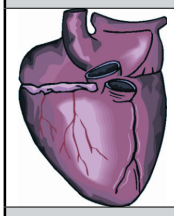
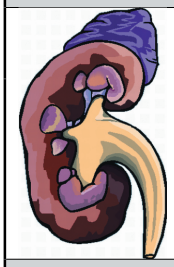
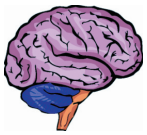
Lipid metabolism/thermogenesis: CB-1 agonists increase lipogenesis (Cota *et al.*, 2003). However, in one study that failed to demonstrate either endocannabinoid receptor in rat adipocytes, WIN55,212 2 was actually found to increase lipolysis (Nieri *et al.*, 2003).

Insulin sensitivity: A direct interplay of the endocannabinoid (EC) system with insulin sensitivity in adipocytes has not yet been described.

Endocrine activity: The EC system and leptin may be functionally linked. The expression of endocannabinoids in the brain is decreased by leptin administration and increased by leptin resistance (Di Marzo *et al.*, 2000). On the other hand, CB-$1^{-/-}$ mice have depressed leptin serum levels, hinting at a negative feedback loop connecting the periphery with the CNS (Cota *et al.*, 2003).

Conclusion: Given the physiological relevance and ther-

Table 2: Regulation of adipose function by direct action of peripheral hormones and neuropeptides

REGULATORS		ADIPOSE FUNCTION						
Systems	**Hormones**	**Insulin Sensitivity**		**Adrenergic Sensitivity**		**Endocrine Activity**		
GASTROINTESTINAL HORMONES		Glucose Uptake	Lipogenesis	Lipolysis	Thermo-genesis	Leptin	Adipo-nectin	Others
	GIP	↑	↑ (↓)	↓ (↑)	?	?	?	?
	GLP-1	↑	↑	↑/↔	?	?	?	?
	Ghrelin	↑/↔	?	↓/↔	↔	?	↓	?
CARDIAC HORMONES		Glucose Uptake	Lipogenesis	Lipolysis	Thermo-genesis	Leptin	Adipo-nectin	Others
	Natriuretic Peptides	↔	?	↑	↔	↑	↔	MCP-1 ↑
RAAS		Glucose Uptake	Lipogenesis	Lipolysis	Thermo-genesis	Leptin	Adipo-nectin	Others
	Angiotensin II	↔	↑	↓/↔/↑	?	↑	?	PAI-1 ↑ IL-6 ↑ IL-8 ↑
	Aldosterone	↓	?	?	↓	↑	?	MCP-1 ↑
NEUROPEPTIDES		Glucose Uptake	Lipogenesis	Lipolysis	Thermo-genesis	Leptin	Adipo-nectin	Others
	α-MSH	?	?	↑	?	↓	?	?
	ACTH	↑/↓	?	↑/ ↔	↑	↓	?	?
	CART	↑	?	?	↑	↑	?	?
	CNTF	↔	?	?	↑	↓	?	?
	Orexins	?	?	?	?	?	?	?
	MCH	?	?	?	?	↑	?	?
	Endocannabinoids	?	↑	↑	?	?	?	?

↑, increased by hormone/neuropeptide

↓, decreased by hormone/neuropeptide

↔, unchanged by by hormone/neuropeptide

?, not established

This table summarizes evidence from *in-vitro* studies.

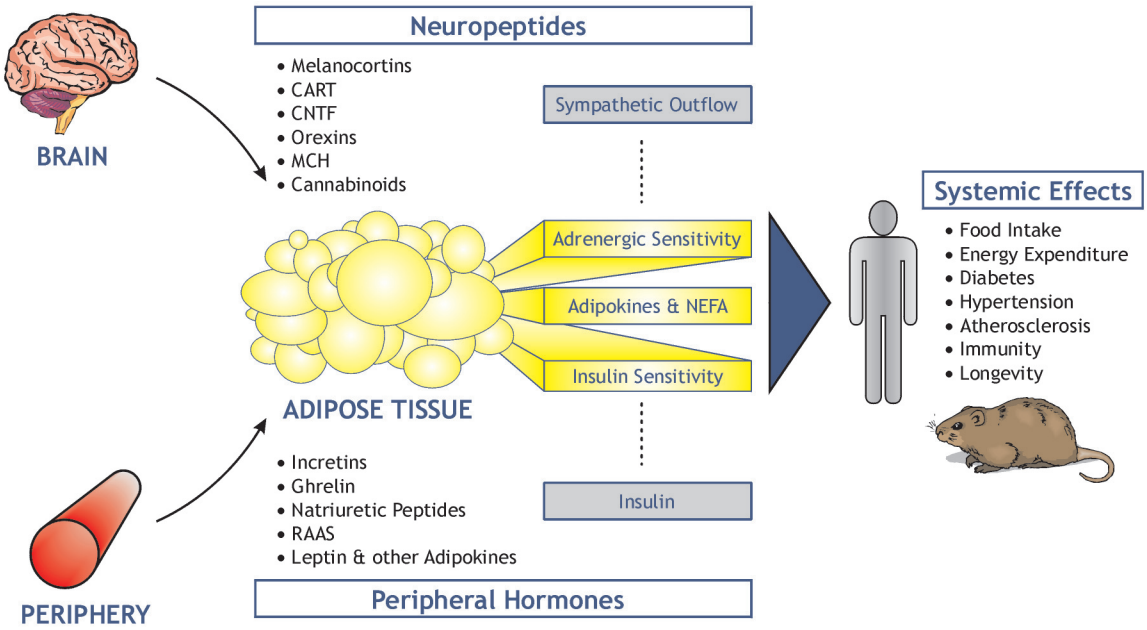


Figure 1: Regulation of adipose tissue physiology
Adipose tissue physiology is modulated by multiple signals. The role of adipose tissue-dependent actions of classical regulators such as insulin and adrenergic transmitters has been studied in mouse models using tissue-specific genetic engineering technology. Recent research has identified a number of novel regulators that influence adipose biology. These comprise neuropeptides and peripheral hormones including adipokines which act in an autocrine/paracrine manner. An accumulating body of data suggests that neuropeptidergic and peripheral hormone interactions impact on the known triad of adipose tissue functions, i. e. adrenergic sensitivity, endocrine activity, and insulin sensitivity. Selective impairment of these adipocyte features results in pleiotropic consequences for whole body physiology. Abreviations: CART, cocaine- and amphetamine-regulated transcript; CNTF, ciliary neurotrophic factor; MCH, melanin-concentrating hormone; NEFA, non-esterified fatty acids; RAAS, renin-angiotensin-aldosterone system.

apeutic potential of the cannabinoid sys-tem for energy homeostasis, more research is clearly needed to define the effects of cannabinoids and their antagonists on adipose tissue.

PERSPECTIVE

Adipocytes play an active role in the control of energy homeostasis. This activity appears to be regulated by multiple humoral and paracrine factors including important neuropeptides and peripheral hormones, hitherto mainly linked to actions in a variety of other physiological systems (Table 2). Whole body energy homeostasis is tightly linked to intact adipocyte function, and modulation of this function appears as a core component in a many disease states (Figure 1). Thus, adipose tissue responses to these regulators may cause or mediate metabolic and cardiovascular disorders that are associated with a disturbed energy balance. Selective targeting of fat tissue (Kolonin *et al.*, 2004) and insulin signaling path-ways (Kaneto *et al.*, 2004) have recently become viable therapeutic options. Along these lines, dissecting signaling pathways and molecular mechnisms that impact on adipocyte biology will not only enhance our understanding of a fascinating organ but may help to find new pharmacological treatments.

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REFERENCES

Ailhaud, G., Fukamizu, A., Massiera, F., Negrel, R., Saint-Marc, P. and Teboul, M. (2000) Angiotensinogen, angiotensin II and adipose tissue development. *International Journal of Obesity and Related Metabolic Disorders* **24** Suppl 4, S33-35.

Ajuwon, K.M., Kuske, J.L., Anderson, D.B., Hancock, D.L., Houseknecht, K.L., Adeola, O. and Spurlock, M.E. (2003) Chronic leptin administration increases serum NEFA in the pig and differentially regulates PPAR expression in adipose tissue. *Journal Nutritional Biochemistry* **14**, 576-583.

An, S., Cutler, G., Zhao, J.J., Huang, S.G., Tian, H., Li, W., Liang, L., Rich, M., Bakleh, A., Du, J., Chen, J.L. and Dai, K. (2001) Identification and characterization of a melanin-concentrating hormone receptor. *Proceedings of the National Academy of Sciences of the United States of*

America **98**, 7576-7581.

Aneja, A., El-Atat, F., McFarlane, S.I. and Sowers, J.R. (2004) Hypertension and obesity. *Recent Progress in Hormone Research* **59**, 169-205.

Aprath-Husmann, I., Rohrig, K., Gottschling-Zeller, H., Skurk, T., Scriba, D., Birgel, M. and Hauner, H. (2001) Effects of leptin on the differentiation and metabolism of human adipocytes. *International Journal of Obesity and Related Metabolic Disorders* **25**, 1465-1470.

Arihara, Z., Takahashi, K., Murakami, O., Totsune, K., Sone, M., Satoh, F., Ito, S. and Mouri, T. (2001) Immunoreactive orexin-A in human plasma. *Peptides* **22**, 139-142.

Arvaniti, K., Ricquier, D., Champigny, O. and Richard, D. (1998) Leptin and corticosterone have opposite effects on food intake and the expression of UCP1 mRNA in brown adipose tissue of lep(ob)/lep(ob) mice. *Endocrinology* **139**, 4000-4003.

Asakawa, A., Inui, A., Kaga, T., Katsuura, G., Fujimiya, M., Fujino, M.A. and Kasuga, M. (2003) Antagonism of ghrelin receptor reduces food intake and body weight gain in mice. *Gut* **52**, 947-952.
Ashton, C.H. (2001) Pharmacology and effects of cannabis: a brief review. *British Journal of Psychiatry* **178**, 101-106.

Asnicar, M.A., Smith, D.P., Yang, D.D., Heiman, M.L., Fox, N., Chen, Y.F., Hsiung, H.M. and Koster, A. (2001) Absence of cocaine- and amphetamine-regulated transcript results in obesity in mice fed a high caloric diet. *Endocrinology* **142**, 4394-4400.

Baba, A.S., Harper, J.M. and Buttery, P.J. (2000) Effects of gastric inhibitory polypeptide, somatostatin and epidermal growth factor on lipogenesis in ovine adipose explants. *Comparative Biochemistry and Physiology. Part B, Biochemistry and Molecular Biology* **127**, 173-182.

Baker, D., Pryce, G., Giovannoni, G. and Thompson, A.J. (2003) The therapeutic potential of cannabis. *Lancet Neurology* **2**, 291-298.

Batkai, S., Pacher, P., Osei-Hyiaman, D., Radaeva, S., Liu, J., Harvey-White, J., Offertaler, L., Mackie, K., Rudd, M.A., Bukoski, R.D. and Kunos, G. (2004) Endocannabinoids acting at cannabinoid-1 receptors regulate cardiovascular function in hypertension. *Circulation* **110**, 1996-2002.

Bays, H., Mandarino, L. and DeFronzo, R.A. (2004) Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. *Journal of Clinical Endocrinology and Metabolism* **89**, 463-478.

Bays, H.E. (2004) Current and investigational antiobesity agents and obesity therapeutic treatment targets. *Obesity Research* **12**, 1197-1211.

Beck, B. and Max, J.P. (1983) Gastric inhibitory polypeptide enhancement of the insulin effect on fatty acid incorporation into adipose tissue in the rat. *Regulatory Peptides* **7**, 3-8.

Beck, B. and Max, J.P. (1988) The effects of gastric inhibitory polypeptide and insulin on fatty acid uptake in adipose tissue are not mediated through cyclic AMP in lean and obese Zucker rats. *Hormone and Metabolic Research* **20**, 24-27.

Bensaid, M., Gary-Bobo, M., Esclangon, A., Maffrand, J.P., Le Fur, G., Oury-Donat, F. and Soubrie, P. (2003) The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. *Molecular Pharmacology* **63**, 908-914.

Bertin, E., Arner, P., Bolinder, J. and Hagstrom-Toft, E. (2001) Action of glucagon and glucagon-like peptide-1-(7-36) amide on lipolysis in human subcutaneous adipose tissue and skeletal muscle *in vivo*. *Journal of Clinical Endocrinology and Metabolism* **86**, 1229-1234.

Blüher, M., Kahn, B.B. and Kahn, C.R. (2003) Extended longevity in mice lacking the insulin receptor in adipose tissue. *Science* **299**, 572-574.

Blüher, S., Moschos, S., Bullen, J., Jr., Kokkotou, E., Maratos-Flier, E., Wiegand, S.J., Sleemann, M.W. and Mantzoros, C.S. (2004a) Ciliary neurotrophic factorAx15 alters energy homeostasis, decreases body weight, and improves metabolic control in diet-induced obese and UCP1-DTA mice. *Diabetes* **53**, 2787-2796.

Blüher, S., Ziotopoulou, M., Bullen, J.W., Jr., Moschos, S.J., Ungsunan, L., Kokkotou, E., Maratos-Flier, E. and Mantzoros, C.S. (2004b) Responsiveness to peripherally administered melanocortins in lean and obese mice. *Diabetes* **53**, 82-90.

Boden, G. and Shulman, G.I. (2002) Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. *European Journal of Clinical Investigation* **32** Suppl 3, 14-23.

Bornstein, S.R., Abu-Asab, M., Glasow, A., Path, G., Hauner, H., Tsokos, M., Chrousos, G.P. and Scherbaum, W.A. (2000) Immunohistochemical and ultrastructural

localization of leptin and leptin receptor in human white adipose tissue and differentiating human adipose cells in primary culture. *Diabetes* **49**, 532-538.

Borowsky, B., Durkin, M.M., Ogozalek, K., Marzabadi, M.R., DeLeon, J., Lagu, B., Heurich, R., Lichtblau, H., Shaposhnik, Z., Daniewska, I., Blackburn, T.P., Branchek, T.A., Gerald, C., Vaysse, P.J. and Forray, C. (2002) Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist. *Nature Medicine* **8**, 825-830.

Boschmann, M., Ringel, J., Klaus, S. and Sharma, A.M. (2001) Metabolic and hemodynamic response of adipose tissue to angiotensin II. *Obesity Research* **9**, 486-491.

Boschmann, M., Jordan, J., Schmidt, S., Adams, F., Luft, F.C. and Klaus, S. (2002) Gender-specific response to interstitial angiotensin II in human white adipose tissue. *Hormone and Metabolic Research* **34**, 726-730.

Boschmann, M., Jordan, J., Adams, F., Christensen, N.J., Tank, J., Franke, G., Stoffels, M., Sharma, A.M., Luft, F.C. and Klaus, S. (2003) Tissue-specific response to interstitial angiotensin II in humans. *Hypertension* **41**, 37-41.

Boston, B.A. and Cone, R.D. (1996) Characterization of melanocortin receptor subtype expression in murine adipose tissues and in the 3T3-L1 cell line. *Endocrinology* **137**, 2043-2050.

Boston, B.A. (1999) The role of melanocortins in adipocyte function. *Annals of the New York Academy of Sciences* **885**, 75-84.

Bousquet-Melou, A., Galitzky, J., Lafontan, M. and Berlan, M. (1995) Control of lipolysis in intra-abdominal fat cells of nonhuman primates: comparison with humans. *Journal of Lipid Research* **36**, 451-461.

Bradley, R.L., Kokkotou, E.G., Maratos-Flier, E. and Cheatham, B. (2000) Melanin-concentrating hormone regulates leptin synthesis and secretion in rat adipocytes. *Diabetes* **49**, 1073-1077.

Bradley, R.L., Cleveland, K.A. and Cheatham, B. (2001) The adipocyte as a secretory organ: mechanisms of vesicle transport and secretory pathways. *Recent Progress in Hormone Research* **56**, 329-358.

Bradley, R.L., Mansfield, J.P., Maratos-Flier, E. and Cheatham, B. (2002) Melanin-concentrating hormone activates signaling pathways in 3T3-L1 adipocytes. American Journal of Physiology. *Endocrinology and Metabolism* **283**, E584-592.

Bullock, B.P., Heller, R.S. and Habener, J.F. (1996) Tissue distribution of messenger ribonucleic acid encoding the rat glucagon-like peptide-1 receptor. *Endocrinology* **137**, 2968-2978.

Buse, J.B., Henry, R.R., Han, J., Kim, D.D., Fineman, M.S. and Baron, A.D. (2004) Effects of ex-enatide (exendin-4) on glycemic control over 30 Weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* **27**, 2628-2635.

Caldiz, C.I. and de Cingolani, G.E. (1999) Insulin resistance in adipocytes from spontaneously hypertensive rats: effect of long-term treatment with enalapril and losartan. *Metabolism: Clinical and Experimental* **48**, 1041-1046.

Cassis, L.A. and Dwoskin, L.P. (1991) Presynaptic modulation of neurotransmitter release by endogenous angiotensin II in brown adipose tissue. *Journal of Neural Transmission*. Supplementum **34**, 129-137.

Cassis, L.A. (1993) Role of angiotensin II in brown adipose thermogenesis during cold acclimation. *American Journal of Physiology* **265**, E860-865.

Cassis, L.A. (1994) Angiotensin II in brown adipose tissue from young and adult Zucker obese and lean rats. *American Journal of Physiology* **266**, E453-458.

Cassis, L.A., English, V.L., Bharadwaj, K. and Boustany, C.M. (2004) Differential effects of local versus systemic angiotensin II in the regulation of leptin release from adipocytes. *Endocrinology* **145**, 169-174.

Chagnon, Y.C., Chen, W.J., Perusse, L., Chagnon, M., Nadeau, A., Wilkison, W.O. and Bouchard, C. (1997) Linkage and association studies between the melanocortin receptors 4 and 5 genes and obesity-related phenotypes in the Quebec Family Study. *Molecular Medicine* **3**, 663-673.

Chernick, S.S., Spooner, P.M., Garrison, M.M. and Scow, R.O. (1986) Effect of epinephrine and other lipolytic agents on intracellular lipolysis and lipoprotein lipase activity in 3T3-L1 adipocytes. *Journal of Lipid Research* **27**, 286-294.

Chhajlani, V. (1996) Distribution of cDNA for melanocortin receptor subtypes in human tissues. *Biochemistry and Molecular Biology International* **38**, 73-80.

Choi, K., Roh, S.G., Hong, Y.H., Shrestha, Y.B., Hishikawa, D., Chen, C., Kojima, M., Kangawa, K. and Sasaki, S. (2003) The role of ghrelin and growth hormone secretagogues receptor on rat adipogenesis. *Endocrinology* **144**, 754-759.

Christiansen, N., Kraus, D., Perwitz, N., Meier, B., Fasshauer, M. and Klein, J. (2005) Direct actions of brain natriuretic peptide (BNP) on brown adipose tissue include stimulation of monocyte chemoattractant protein-1 (MCP-1), angiotensin II, and leptin. *Experimental and Clinical Endocrinology and Diabetes* **113**, S5.

Claycombe, K.J., Xue, B.Z., Mynatt, R.L., Zemel, M.B. and Moustaid-Moussa, N. (2000) Regulation of leptin by agouti. *Physiological Genomics* **2**, 101-105.

Clement, K., Vaisse, C., Manning, B.S.J., Basdevant, A., Guy-Grand, B., Ruiz, J., Silver, K.D., Shuldiner, A.R., Froguel, P. and Strosberg, A.D. (1995) Genetic variation in the beta3-adrenergic receptor and an increased capacity to gain weight in patients with morbid obesity. *New England Journal of Medicine* **333**, 352-354.

Commins, S.P., Watson, P.M., Padgett, M.A., Dudley, A., Argyropoulos, G. and Gettys, T.W. (1999) Induction of uncoupling protein expression in brown and white adipose tissue by leptin. *Endocrinology* **140**, 292-300.

Cooper, M.E. (2004) The role of the renin-angiotensin-aldosterone system in diabetes and its vascular complications. *American Journal of Hypertension* **17**, 16S-20S; quiz A12-14.
Corry, D.B. and Tuck, M.L. (2003) The effect of aldosterone on glucose metabolism. *Current Hypertension Reports* **5**, 106-109.

Cota, D., Marsicano, G., Tschop, M., Grubler, Y., Flachskamm, C., Schubert, M., Auer, D., Yas-souridis, A., Thone-Reineke, C., Ortmann, S., Tomassoni, F., Cervino, C., Nisoli, E., Linthorst, A.C., Pasquali, R., Lutz, B., Stalla, G.K. and Pagotto, U. (2003) The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *Journal of Clinical Investigation* **112**, 423-431.

Crandall, D.L., Ferraro, G.D. and Cervoni, P. (1989) Effect of experimental obesity and subsequent weight reduction upon circulating atrial natriuretic peptide. *Proceedings of the Society for Experimental Biology and Medicine* **191**, 352-356.

Crilley, C.T. and Garcia, R. (1997) Effects of atrial natriuretic factor on glucose metabolism in isolated adipocytes. *Regulatory Peptides* **68**, 125-130.

Croci, T., Manara, L., Aureggi, G., Guagnini, F., Rinaldi-Carmona, M., Maffrand, J.P., Le Fur, G., Mukenge, S. and Ferla, G. (1998) *In vitro* functional evidence of neuronal cannabinoid CB1 receptors in human ileum. *British Journal of Pharmacology* **125**, 1393-1395.

Cummings, D.E. and Schwartz, M.W. (2000) Melanocortins and body weight: a tale of two receptors. *Nature Genetics* **26**, 8-9.

Cusin, I., Zakrzewska, K.E., Boss, O., Muzzin, P., Giacobino, J.P., Ricquier, D., Jeanrenaud, B. and Rohner-Jeanrenaud, F. (1998) Chronic central leptin infusion enhances insulin-stimulated glucose metabolism and favors the expression of uncoupling proteins. *Diabetes* **47**, 1014-1019.

Dahlof, B., Devereux, R.B., Kjeldsen, S.E., Julius, S., Beevers, G., de Faire, U., Fyhrquist, F., Ibsen, H., Kristiansson, K., Lederballe-Pedersen, O., Lindholm, L.H., Nieminen, M.S., Omvik, P., Oparil, S. and Wedel, H. (2002) Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint Reduction in Hypertension study (LIFE): a randomised trial against atenolol. *Lancet* **359**, 995-1003.

Das, S.K., Paria, B.C., Chakraborty, I. and Dey, S.K. (1995) Cannabinoid ligand-receptor signaling in the mouse uterus. *Proceedings of the National Academy of Sciences of the United States of America* **92**, 4332-4336.

Delporte, M.L., El Mkadem, S.A., Quisquater, M. and Brichard, S.M. (2004) Leptin treatment markedly increased plasma adiponectin but barely decreased plasma resistin of ob/ob mice. American Journal of Physiology. *Endocrinology and Metabolism* **287**, E446-453.
Dessi-Fulgheri, P., Sarzani, R. and Rappelli, A. (1998) The natriuretic peptide system in obesity-related hypertension: new pathophysiological aspects. *J Nephrol* **11**, 296-299.

Di Marzo, V., Breivogel, C.S., Tao, Q., Bridgen, D.T., Razdan, R.K., Zimmer, A.M., Zimmer, A. and Martin, B.R. (2000) Levels, metabolism, and pharmacological activity of anandamide in CB(1) cannabinoid receptor knockout mice: evidence for non-CB(1), non-CB(2) receptor-mediated actions of anandamide in mouse brain. *Journal of Neurochemistry* **75**, 2434-2444.

Digby, J.E., Montague, C.T., Sewter, C.P., Sanders, L., Wilkison, W.O., O'Rahilly, S. and Prins, J.B. (1998) Thiazolidinedione exposure increases the expression of uncoupling protein 1 in cultured human preadipocytes. *Diabetes* **47**, 138-141.

Dinulescu, D.M. and Cone, R.D. (2000) Agouti and agouti-related protein: analogies and contrasts. *Journal of Biological Chemistry* **275**, 6695-6698.

Doggrell, S.A. (2003) Does the melanin-concentrating hormone antagonist SNAP-7941 deserve 3As? *Expert Opinion on Investigational Drugs* **12**, 1035-1038.

Dominguez, G., Vicentic, A., Del Giudice, E.M., Jaworski, J., Hunter, R.G. and Kuhar, M.J. (2004) CART Peptides: modulators of mesolimbic dopamine, feeding, and stress. *Annals of the New York Academy of Sciences* **1025**, 363-369.

Drewes, C., Nauck, M.A., Horn, R., Holst, J., Schmiegel, W. and Brabant, G. (1997) A liquid mixed meal or exogenous glucagon-like peptide 1 (GLP-1) do not alter plasma leptin concentra-tions in healthy volunteers. *Acta Diabetologica* **34**, 230-234.

Drucker, D.J. (2001) Minireview: the glucagon-like peptides. *Endocrinology* **142**, 521-527.

Drucker, D.J. (2002) Biological actions and therapeutic potential of the glucagon-like peptides. *Gastroenterology* **122**, 531-544.

Drucker, D.J. (2003a) Enhancing incretin action for the treatment of type 2 diabetes. *Diabetes Care* **26**, 2929-2940.

Drucker, D.J. (2003b) Therapeutic potential of dipeptidyl peptidase IV inhibitors for the treatment of type 2 diabetes. *Expert Opinion on Investigational Drugs* **12**, 87-100.

Dupre, J., Greenidge, N., McDonald, T.J., Ross, S.A. and Rubinstein, D. (1976) Inhibition of ac-tions of glucagon in adipocytes by gastric inhibitory polypeptide. *Metabolism: Clinical and Experimental* **25**, 1197-1199.

Ebihara, K., Masuzaki, H. and Nakao, K. (2004) Long-term leptin-replacement therapy for lipoatrophic diabetes. *New England Journal of Medicine* **351**, 615-616.

Eckel, R.H., Fujimoto, W.Y. and Brunzell, J.D. (1979) Gastric inhibitory polypeptide enhanced lipoprotein lipase activity in cultured preadipocytes. *Diabetes* **28**, 1141-1142.

Egan, J.M., Montrose-Rafizadeh, C., Wang, Y., Bernier, M. and Roth, J. (1994) Glucagon-like peptide-1(7-36) amide (GLP-1) enhances insulin-stimulated glucose metabolism in 3T3-L1 adipocytes: one of several potential extrapancreatic sites of GLP-1 action. *Endocrinology* **135**, 2070-2075.

Ehrhart-Bornstein, M., Lamounier-Zepter, V., Schraven, A., Langenbach, J., Willenberg, H.S., Barthel, A., Hauner, H., McCann, S.M., Scherbaum, W.A. and Bornstein, S.R. (2003) Human adipocytes secrete mineralocorticoid-releasing factors. *Proceedings of the National Academy of Sci-ences of the United States of America* **100**, 14211-14216.

Ehses, J.A., Lee, S.S., Pederson, R.A. and McIntosh, C.H. (2001) A new pathway for glucose-dependent insulinotropic polypeptide (GIP) receptor signaling: evidence for the involvement of phospholipase A2 in GIP-stimulated insulin secretion. *Journal of Biological Chemistry* **276**, 23667-23673.

Ehses, J.A., Pelech, S.L., Pederson, R.A. and McIntosh, C.H. (2002) Glucose-dependent insulinotropic polypeptide activates the Raf-Mek1/2-ERK1/2 module via a cyclic AMP/cAMP-dependent protein kinase/Rap1-mediated pathway. *Journal of Biological Chemistry* **277**, 37088-37097.

Elimam, A., Kamel, A. and Marcus, C. (2002) *In vitro* effects of leptin on human adipocyte metabolism. *Hormone Research* **58**, 88-93.

Ellacott, K.L. and Cone, R.D. (2004) The central melanocortin system and the integration of short- and long-term regulators of energy homeostasis. *Recent Progress in Hormone Research* **59**, 395-408.

Engeli, S., Schling, P., Gorzelniak, K., Boschmann, M., Janke, J., Ailhaud, G., Teboul, M., Massiera, F. and Sharma, A.M. (2003) The adipose-tissue renin-angiotensin-aldosterone system: role in the metabolic syndrome? *International Journal of Biochemistry and Cell Biology* **35**, 807-825.

Fain, J.N., Kanu, A., Bahouth, S.W., Cowan, G.S. and Lloyd Hiler, M. (2003) Inhibition of leptin release by atrial natriuretic peptide (ANP) in human adipocytes. *Biochemical Pharmacology* **65**, 1883-1888.

Fasshauer, M. and Paschke, R. (2003) Regulation of adipocytokines and insulin resistance. *Diabetologia* **46**, 1594-1603.

Fasshauer, M., Klein, J., Kralisch, S., Klier, M., Lossner, U., Bluher, M. and Paschke, R. (2004) Growth hormone is a positive regulator of adiponectin receptor 2 in 3T3-L1 adipocytes. *FEBS Letters* **558**, 27-32.

Flint, A., Raben, A., Rehfeld, J.F., Holst, J.J. and Astrup, A. (2000) The effect of glucagon-like peptide-1 on energy expenditure and substrate metabolism in humans. *International Journal of Obesity and Related Metabolic Disorders* **24**, 288-298.

Forbes, S., Bui, S., Robinson, B.R., Hochgeschwender, U. and Brennan, M.B. (2001) Integrated control of appetite and fat metabolism by the leptin-proopiomelanocortin pathway. *Proceedings of the National Academy of Sciences of the United States of America* **98**, 4233-4237.

Fruebis, J., Tsao, T.S., Javorschi, S., Ebbets-Reed, D., Erickson, M.R., Yen, F.T., Bihain, B.E. and Lodish, H.F. (2001) Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proceedings of the National Academy of Sciences of the United States of America* **98**, 2005-2010.

Frühbeck, G., Aguado, M., Gomez-Ambrosi, J. and Martinez, J.A. (1998) Lipolytic effect of *in vivo* leptin administration on adipocytes of lean and ob/ob mice, but not db/db mice. *Biochemical and Biophysical Research*

Communications **250**, 99-102.

Frühbeck, G., Gomez-Ambrosi, J., Muruzabal, F.J. and Burrell, M.A. (2001) The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. *American Journal of Physiology. Endocrinology and Metabolism* **280**, E827-847.

Frühbeck, G. and Gomez-Ambrosi, J. (2002) Depot-specific differences in the lipolytic effect of leptin on isolated white adipocytes. *Med Sci Monit* **8**, BR47-55.

Fujimoto, M., Masuzaki, H., Tanaka, T., Yasue, S., Tomita, T., Okazawa, K., Fujikura, J., Chusho, H., Ebihara, K., Hayashi, T., Hosoda, K. and Nakao, K. (2004) An angiotensin II AT1 receptor antagonist, telmisartan augments glucose uptake and GLUT4 protein expression in 3T3-L1 adipocytes. *FEBS Letters* **576**, 492-497.

Fumeron, F., Durack-Bown, I., Betoulle, D., Cassard-Doulcier, A.M., Tuzet, S., Bouillaud, F., Melchior, J.C., Ricquier, D. and Apfelbaum, M. (1996) Polymorphisms of uncoupling protein (UCP) and beta 3 adrenoreceptor genes in obese people submitted to a low calorie diet. *International Journal of Obesity and Related Metabolic Disorders* **20**, 1051-1054.

Garg, A. (2004) Acquired and inherited lipodystrophies. *New England Journal of Medicine* **350**, 1220-1234.

Garruti, G. and Ricquier, D. (1992) Analysis of uncoupling protein and its mRNA in adipose tissue deposits of adult humans. *International Journal of Obesity and Related Metabolic Disorders* **16**, 383-390.

Gavrila, A., Chan, J.L., Miller, L.C., Heist, K., Yiannakouris, N. and Mantzoros, C.S. (2005) Circulating melanin-concentrating hormone (MCH), agouti-related protein (AGRP), and α- melanocyte-stimulating hormone levels in relation to body composition; alterations in response to food deprivation and recombinant human leptin administration. *Journal of Clinical Endocrinology and Metabo-lism* **90**, 1047-1054

Ghilardi, N., Ziegler, S., Wiestner, A., Stoffel, R., Heim, M.H. and Skoda, R.C. (1996) Defective STAT signaling by the leptin receptor in diabetic mice. *Proceedings of the National Academy of Sciences of the United States of America* **93**, 6231-6235.

Giacchetti, G., Faloia, E., Sardu, C., Camilloni, M.A., Mariniello, B., Gatti, C., Garrapa, G.G., Guerrieri, M. and Mantero, F. (2000) Gene expression of angiotensinogen in adipose tissue of obese patients. *International Journal of Obesity and Related Metabolic Disorders* **24** Suppl 2, S142-143.

Goldstein, B.J. and Scalia, R. (2004) Adiponectin: A novel adipokine linking adipocytes and vascular function. *Journal of Clinical Endocrinology and Metabolism* **89**, 2563-2568.

Gomez-Ambrosi, J., Frühbeck, G. and Martinez, J.A. (1999) Leptin, but not a beta 3-adrenergic agonist, upregulates muscle uncoupling protein-3 messenger RNA expression: short-term thermogenic interactions. *Cellular and Molecular Life Sciences* **55**, 992-997.

Goodfriend, T.L., Egan, B.M. and Kelley, D.E. (1998) Aldosterone in obesity. *Endocrine Research* **24**, 789-796.

Goossens, G.H., Blaak, E.E. and van Baak, M.A. (2003) Possible involvement of the adipose tissue renin-angiotensin system in the pathophysiology of obesity and obesity-related disorders. *Obesity Reviews* **4**, 43-55.

Grunfeld, C., Hagman, J., Sabin, E.A., Buckley, D.I., Jones, D.S. and Ramachandran, J. (1985) Characterization of adrenocorticotropin receptors that appear when 3T3-L1 cells differentiate into adipocytes. *Endocrinology* **116**, 113-117.

Haluzik, M., Sindelka, G., Widimsky, J., Jr., Prazny, M., Zelinka, T. and Skrha, J. (2002) Serum leptin levels in patients with primary hyperaldosteronism before and after treatment: relationships to insulin sensitivity. *Journal of Human Hypertension* **16**, 41-45.

Hauner, H., Glatting, G., Kaminska, D. and Pfeiffer, E.F. (1988) Effects of gastric inhibitory polypeptide on glucose and lipid metabolism of isolated rat adipocytes. *Annals of Nutrition and Metabolism* **32**, 282-288.

Hausberg, M., Morgan, D.A., Mitchell, J.L., Sivitz, W.I., Mark, A.L. and Haynes, W.G. (2002) Leptin potentiates thermogenic sympathetic responses to hypothermia: a receptor-mediated effect. *Diabetes* **51**, 2434-2440.

Havel, P.J. (2004) Update on adipocyte hormones: regulation of energy balance and carbohydrate/lipid metabolism. *Diabetes* **53** Suppl 1, S143-151.

Haynes, A.C., Jackson, B., Chapman, H., Tadayyon, M., Johns, A., Porter, R.A. and Arch, J.R. (2000) A selective orexin-1 receptor antagonist reduces food consumption in male and female rats. *Regulatory Peptides* **96**, 45-51.

Haynes, A.C., Chapman, H., Taylor, C., Moore, G.B., Cawthorne, M.A., Tadayyon, M., Clapham, J.C. and Arch, J.R. (2002) Anorectic, thermogenic and anti-obesity activity of a selective orexin-1 receptor antagonist in ob/ob mice. *Regulatory Peptides* **104**, 153-159.

Hill, J., Duckworth, M., Murdock, P., Rennie, G., Sabido-

David, C., Ames, R.S., Szekeres, P., Wilson, S., Bergsma, D.J., Gloger, I.S., Levy, D.S., Chambers, J.K. and Muir, A.I. (2001) Molecular cloning and functional characterization of MCH2, a novel human MCH receptor. *Journal of Biological Chemistry* **276**, 20125-20129.

Hoggard, N., Hunter, L., Duncan, J.S. and Rayner, D.V. (2004a) Regulation of adipose tissue leptin secretion by alpha-melanocyte-stimulating hormone and agouti-related protein: further evidence of an interaction between leptin and the melanocortin signalling system. *Journal of Molecular Endocrinology* **32**, 145-153.

Hoggard, N., Johnstone, A.M., Faber, P., Gibney, E.R., Elia, M., Lobley, G., Rayner, V., Horgan, G., Hunter, L., Bashir, S. and Stubbs, R.J. (2004b) Plasma concentrations of alpha-MSH, AgRP and leptin in lean and obese men and their relationship to differing states of energy balance perturbation. *Clinical Endocrinology* **61**, 31-39.

Horvath, T.L., Diano, S. and Tschop, M. (2004) Brain circuits regulating energy homeostasis. *Neuroscientist* **10**, 235-246.

Huan, J.N., Li, J., Han, Y., Chen, K., Wu, N. and Zhao, A.Z. (2003) Adipocyte-selective reduction of the leptin receptors induced by antisense RNA leads to increased adiposity, dyslipidemia, and insulin resistance. *Journal of Biological Chemistry* **278**, 45638-45650.

Hukshorn, C.J., van Dielen, F.M., Buurman, W.A., Westerterp-Plantenga, M.S., Campfield, L.A. and Saris, W.H. (2002) The effect of pegylated recombinant human leptin (PEG-OB) on weight loss and inflammatory status in obese subjects. *International Journal of Obesity and Related Metabolic Disorders* **26**, 504-509.

Hunter, R.G., Philpot, K., Vicentic, A., Dominguez, G., Hubert, G.W. and Kuhar, M.J. (2004) CART in feeding and obesity. *Trends in Endocrinology and Metabolism* **15**, 454-459.

Ishii, Y., Blundell, J.E., Halford, J.C., Upton, N., Porter, R., Johns, A., Jeffrey, P., Summerfield, S. and Rodgers, R.J. (2005) Anorexia and weight loss in male rats 24h following single dose treatment with orexin-1 receptor antagonist SB-334867. *Behavioural Brain Research* **157**, 331-341.

Ito, M., Gomori, A., Ishihara, A., Oda, Z., Mashiko, S., Matsushita, H., Yumoto, M., Sano, H., To-kita, S., Moriya, M., Iwaasa, H. and Kanatani, A. (2003) Characterization of MCH-mediated obesity in mice. American Journal of Physiology. *Endocrinology and Metabolism* **284**, E940-945.

Jaeger, J., Perwitz, N., Ott, V., Meier, B., Fehm, H.L., Fasshauer, M. and Klein, J. (2003) Aldosterone directly modulates adipocyte metabolism and adipokine expression in a brown adipocyte model. The Endocrine Society's 85th Annual Meeting (Abstract).

Janke, J., Engeli, S., Gorzelniak, K., Luft, F.C. and Sharma, A.M. (2002) Mature adipocytes inhibit *in vitro* differentiation of human preadipocytes via angiotensin type 1 receptors. *Diabetes* **51**, 1699-1707.

Jeandel, L., Okamura, H., Belles-Isles, M., Chabot, J.G., Dihl, F., Morel, G., Kelly, P.A. and Heisler, S. (1989) Immunocytochemical localization, binding, and effects of atrial natriuretic peptide in rat adipocytes. *Molecular and Cellular Endocrinology* **62**, 69-78.

Jensen, P.B., Kristensen, P., Clausen, J.T., Judge, M.E., Hastrup, S., Thim, L., Wulff, B.S., Foged, C., Jensen, J., Holst, J.J. and Madsen, O.D. (1999) The hypothalamic satiety peptide CART is expressed in anorectic and non-anorectic pancreatic islet tumors and in the normal islet of Langer-hans. *FEBS Letters* **447**, 139-143.

Jöhren, O., Brüggemann, N. and Dominiak, P. (2004) Orexins (hypocretins) and adrenal function. *Hormone and Metabolic Research* **36**, 370-375.

Jones, B.H., Standridge, M.K. and Moustaid, N. (1997) Angiotensin II increases lipogenesis in 3T3-L1 and human adipose cells. *Endocrinology* **138**, 1512-1519.

Kalra, P.R. and Tigas, S. (2002) Regulation of lipolysis: natriuretic peptides and the development of cachexia. *International Journal of Cardiology* **85**, 125-132.

Kamohara, S., Burcelin, R., Halaas, J.L., Friedman, J.M. and Charron, M.J. (1997) Acute stimulation of glucose metabolism in mice by leptin treatment. *Nature* **389**, 374-377.

Kaneto, H., Nakatani, Y., Miyatsuka, T., Kawamori, D., Matsuoka, T.A., Matsuhisa, M., Kajimoto, Y., Ichijo, H., Yamasaki, Y. and Hori, M. (2004) Possible novel therapy for diabetes with cell-permeable JNK-inhibitory peptide. *Nature Medicine* **10**, 1128-1132.

Kastin, A.J., Redding, T.W., Hall, R., Besser, G.M. and Schally, A.V. (1975) Lipid mobilizing hormones of the hypothalamus and pituitary. *Pharmacology, Biochemistry and Behavior* **3**, 121-126.

Katsuki, A., Sumida, Y., Murashima, S., Furuta, M., Araki-Sasaki, R., Tsuchihashi, K., Hori, Y., Yano, Y. and Adachi, Y. (2000) Elevated plasma levels of alpha-melanocyte stimulating hormone (alpha-MSH) are correlated with insulin resistance in obese men. *International Journal of Obesity and Related Metabolic Disorders* **24**, 1260-1264.

Katsuki, A., Sumida, Y., Gabazza, E.C., Murashima, S., Tanaka, T., Furuta, M., Araki-Sasaki, R., Hori, Y., Nakatani, K., Yano, Y. and Adachi, Y. (2001) Plasma levels of agouti-related protein are increased in obese men. *Journal of Clinical Endocrinology and Metabolism* **86**, 1921-1924.

Kershaw, E.E. and Flier, J.S. (2004) Adipose tissue as an endocrine organ. *Journal of Clinical Endocrinology and Metabolism* **89**, 2548-2556.

Kim, M.S., Yoon, C.Y., Jang, P.G., Park, Y.J., Shin, C.S., Park, H.S., Ryu, J.W., Pak, Y.K., Park, J.Y., Lee, K.U., Kim, S.Y., Lee, H.K., Kim, Y.B. and Park, K.S. (2004) The mitogenic and anti-apoptotic actions of ghrelin in 3T3-L1 adipocytes. *Molecular Endocrinology* **18**, 2291-2301.

Kim, S., Whelan, J., Claycombe, K., Reath, D.B. and Moustaid-Moussa, N. (2002) Angiotensin II increases leptin secretion by 3T3-L1 and human adipocytes via a prostaglandin-independent mechanism. *Journal of Nutrition* **132**, 1135-1140.

Kiwaki, K. and Levine, J.A. (2003) Differential effects of adrenocorticotropic hormone on human and mouse adipose tissue. *Journal of Comparative Physiology. B, Biochemical, Systemic, and Environmental Physiology* **173**, 675-678.

Klein, J., Fasshauer, M., Benito, M. and Kahn, C.R. (2000) Insulin and the beta3-adrenoceptor differentially regulate uncoupling protein-1 expression. *Molecular Endocrinology* **14**, 764-773.

Klein, J., Fasshauer, M., Klein, H.H., Benito, M. and Kahn, C.R. (2002) Novel adipocyte lines from brown fat: a model system for the study of differentiation, energy metabolism, and insulin action. *Bioessays* **24**, 382-388.

Klein, T.W., Newton, C., Larsen, K., Lu, L., Perkins, I., Nong, L. and Friedman, H. (2003) The cannabinoid system and immune modulation. *Journal of Leukocyte Biology* **74**, 486-496.

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.

Kokkotou, E.G., Tritos, N.A., Mastaitis, J.W., Slieker, L. and Maratos-Flier, E. (2001) Melanin-concentrating hormone receptor is a target of leptin action in the mouse brain. *Endocrinology* **142**, 680-686.

Kolonin, M.G., Saha, P.K., Chan, L., Pasqualini, R. and Arap, W. (2004) Reversal of obesity by targeted ablation of adipose tissue. *Nature Medicine* **10**, 625-632.

Kong, W.M., Stanley, S., Gardiner, J., Abbott, C., Murphy, K., Seth, A., Connoley, I., Ghatei, M., Stephens, D. and Bloom, S. (2003) A role for arcuate cocaine and amphetamine-regulated transcript in hyperphagia, thermogenesis, and cold adaptation. *FASEB Journal* **17**, 1688-1690.

Korbonits, M., Goldstone, A.P., Gueorguiev, M. and Grossman, A.B. (2004) Ghrelin—a hormone with multiple functions. *Frontiers in Neuroendocrinology* **25**, 27-68.

Korner, J. and Aronne, L.J. (2004) Pharmacological approaches to weight reduction: therapeutic targets. *Journal of Clinical Endocrinology and Metabolism* **89**, 2616-2621.

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.

Kraus, D., Fasshauer, M., Ott, V., Meier, B., Jost, M., Klein, H.H. and Klein, J. (2002) Leptin secretion and negative autocrine crosstalk with insulin in brown adipocytes. *Journal of Endocrinology* **175**, 185-191.

Kubota, A., Yamada, Y., Yasuda, K., Someya, Y., Ihara, Y., Kagimoto, S., Watanabe, R., Kuroe, A., Ishida, H. and Seino, Y. (1997) Gastric inhibitory polypeptide activates MAP kinase through the wortmannin-sensitive and -insensitive pathways. *Biochemical and Biophysical Research Communications* **235**, 171-175.

Kuroda, M., Honnor, R.C., Cushman, S.W., Londos, C. and Simpson, I.A. (1987) Regulation of insulin-stimulated glucose transport in the isolated rat adipocyte. cAMP-independent effects of lipolytic and antilipolytic agents. *Journal of Biological Chemistry* **262**, 245-253.

Kwon, H.Y., Bultman, S.J., Loffler, C., Chen, W.J., Furdon, P.J., Powell, J.G., Usala, A.L., Wilkison, W., Hansmann, I. and Woychik, R.P. (1994) Molecular structure and chromosomal mapping of the human homolog of the agouti gene. *Proceedings of the National Academy of Sciences of the United States of America* **91**, 9760-9764.

Le Menuet, D., Viengchareun, S., Muffat-Joly, M., Zennaro, M.C. and Lombes, M. (2004) Expression and function of the human mineralocorticoid receptor: lessons from transgenic mouse models. *Molecular and Cellular Endocrinology* **217**, 127-136.

Ledent, C., Valverde, O., Cossu, G., Petitet, F., Aubert,

J.F., Beslot, F., Bohme, G.A., Imperato, A., Pedrazzini, T., Roques, B.P., Vassart, G., Fratta, W. and Parmentier, M. (1999) Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. *Science* **283**, 401-404.

Levin, E.R., Gardner, D.G. and Samson, W.K. (1998) Natriuretic peptides. *New England Journal of Medicine* **339**, 321-328.

Lewis, G.F., Carpentier, A., Adeli, K. and Giacca, A. (2002) Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocrine Reviews* **23**, 201-229.

Maeda, N., Shimomura, I., Kishida, K., Nishizawa, H., Matsuda, M., Nagaretani, H., Furuyama, N., Kondo, H., Takahashi, M., Arita, Y., Komuro, R., Ouchi, N., Kihara, S., Tochino, Y., Okutomi, K., Horie, M., Takeda, S., Aoyama, T., Funahashi, T. and Matsuzawa, Y. (2002) Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nature Medicine* **8**, 731-737.

Marette, A. and Bukowiecki, L.J. (1990) Mechanism of norepinephrine stimulation of glucose transport in isolated rat brown adipocytes. *International Journal of Obesity* **14**, 857-867.

Margetic, S., Gazzola, C., Pegg, G.G. and Hill, R.A. (2002) Leptin: a review of its peripheral actions and interactions. *International Journal of Obesity and Related Metabolic Disorders* **26**, 1407-1433.

Marsh, D.J., Weingarth, D.T., Novi, D.E., Chen, H.Y., Trumbauer, M.E., Chen, A.S., Guan, X.M., Jiang, M.M., Feng, Y., Camacho, R.E., Shen, Z., Frazier, E.G., Yu, H., Metzger, J.M., Kuca, S.J., Shearman, L.P., Gopal-Truter, S., MacNeil, D.J., Strack, A.M., MacIntyre, D.E., Van der Ploeg, L.H. and Qian, S. (2002) Melanin-concentrating hormone 1 receptor-deficient mice are lean, hyperactive, and hyperphagic and have altered metabolism. *Proceedings of the National Academy of Sciences of the United States of America* **99**, 3240-3245.

Martinez, J.A., Aguado, M. and Frühbeck, G. (2000) Interactions between leptin and NPY affecting lipid mobilization in adipose tissue. *Journal of Physiology and Biochemistry* **56**, 1-8.

Massa, F., Marsicano, G., Hermann, H., Cannich, A., Monory, K., Cravatt, B.F., Ferri, G.L., Sibaev, A., Storr, M. and Lutz, B. (2004) The endogenous cannabinoid system protects against colonic inflammation. *Journal of Clinical Investigation* **113**, 1202-1209.

Matsuoka, N., Saito, Y., Shirai, K., Kumagai, A., Okuda, H. and Fujii, S. (1978) Studies on the mechanism of action of ACTH on triglyceride synthesis in fat cells. *Endocrinologia Japonica* **25**, 225-229.

McCord, J., Mundy, B.J., Hudson, M.P., Maisel, A.S., Hollander, J.E., Abraham, W.T., Steg, P.G., Omland, T., Knudsen, C.W., Sandberg, K.R. and McCullough, P.A. (2004) Relationship between obesity and B-type natriuretic peptide levels. *Archives of Internal Medicine* **164**, 2247-2252.

Meier, J.J., Nauck, M.A., Schmidt, W.E. and Gallwitz, B. (2002) Gastric inhibitory polypeptide: the neglected incretin revisited. *Regulatory Peptides* **107**, 1-13.

Merida, E., Delgado, E., Molina, L.M., Villanueva-Penacarrillo, M.L. and Valverde, I. (1993) Presence of glucagon and glucagon-like peptide-1-(7-36)amide receptors in solubilized membranes of human adipose tissue. *Journal of Clinical Endocrinology and Metabolism* **77**, 1654-1657.

Mick, G., Vanderbloomer, T., Fu, C.L. and McCormick, K. (1998) Leptin does not affect adipocyte glucose metabolism: studies in fresh and cultured adipocytes. *Metabolism: Clinical and Experimental* **47**, 1360-1365.

Miki, H., Namba, M., Nishimura, T., Mineo, I., Matsumura, T., Miyagawa, J., Nakajima, H., Kuwajima, M., Hanafusa, T. and Matsuzawa, Y. (1996) Glucagon-like peptide-1(7-36)amide enhances insulin-stimulated glucose uptake and decreases intracellular cAMP content in isolated rat adipocytes. *Biochimica et Biophysica Acta* **1312**, 132-136.

Minokoshi, Y., Kahn, C.R. and Kahn, B.B. (2003) Tissue-specific ablation of the GLUT4 glucose transporter or the insulin receptor challenges assumptions about insulin action and glucose homeostasis. *Journal of Biological Chemistry* **278**, 33609-33612.

Miyawaki, K., Yamada, Y., Ban, N., Ihara, Y., Tsukiyama, K., Zhou, H., Fujimoto, S., Oku, A., Tsuda, K., Toyokuni, S., Hiai, H., Mizunoya, W., Fushiki, T., Holst, J.J., Makino, M., Tashita, A., Kobara, Y., Tsubamoto, Y., Jinnouchi, T., Jomori, T. and Seino, Y. (2002) Inhibition of gastric in-hibitory polypeptide signaling prevents obesity. *Nature Medicine* **8**, 738-742.

Montrose-Rafizadeh, C., Yang, H., Wang, Y., Roth, J., Montrose, M.H. and Adams, L.G. (1997) Novel signal transduction and peptide specificity of glucagon-like peptide receptor in 3T3-L1 adipocytes. *Journal of Cellular Physiology* **172**, 275-283.

Morimoto, C., Tsujita, T. and Okuda, H. (1998) Antilipolytic actions of insulin on basal and hormone-induced lipolysis in rat adipocytes. *Journal of Lipid Research*

39, 957-962.

Moro, C., Crampes, F., Sengenes, C., De Glisezinski, I., Galitzky, J., Thalamas, C., Lafontan, M. and Berlan, M. (2004a) Atrial natriuretic peptide contributes to physiological control of lipid mobilization in humans. *FASEB Journal* **18**, 908-910.

Moro, C., Galitzky, J., Sengenes, C., Crampes, F., Lafontan, M. and Berlan, M. (2004b) Functional and pharmacological characterization of the natriuretic peptide-dependent lipolytic pathway in human fat cells. *Journal of Pharmacology and Experimental Therapeutics* **308**, 984-992.

Mountjoy, K.G. and Wong, J. (1997) Obesity, diabetes and functions for proopiomelanocortin-derived peptides. *Molecular and Cellular Endocrinology* **128**, 171-177.

Müller, G., Ertl, J., Gerl, M. and Preibisch, G. (1997) Leptin impairs metabolic actions of insulin in isolated rat adipocytes. *Journal of Biological Chemistry* **272**, 10585-10593.

Murakami, T., Yamashita, T., Iida, M., Kuwajima, M. and Shima, K. (1997) A short form of leptin receptor performs signal transduction. *Biochemical and Biophysical Research Communications* **231**, 26-29.

Murphy, K.G., Abbott, C.R., Mahmoudi, M., Hunter, R., Gardiner, J.V., Rossi, M., Stanley, S.A., Ghatei, M.A., Kuhar, M.J. and Bloom, S.R. (2000) Quantification and synthesis of cocaine- and amphetamine-regulated transcript peptide (79-102)-like immunoreactivity and mRNA in rat tissues. *Journal of Endocrinology* **166**, 659-668.

Mynatt, R.L., Miltenberger, R.J., Klebig, M.L., Zemel, M.B., Wilkinson, J.E., Wilkinson, W.O. and Woychik, R.P. (1997) Combined effects of insulin treatment and adipose tissue-specific agouti expression on the development of obesity. *Proceedings of the National Academy of Sciences of the United States of America* **94**, 919-922.

Nam, S.Y., Kratzsch, J., Kim, K.W., Kim, K.R., Lim, S.K. and Marcus, C. (2001) Cerebrospinal fluid and plasma concentrations of leptin, NPY, and alpha-MSH in obese women and their relation-ship to negative energy balance. *Journal of Clinical Endocrinology and Metabolism* **86**, 4849-4853.

Newby, D., Gertler, A. and Vernon, R.G. (2001) Effects of recombinant ovine leptin on *in vitro* lipolysis and lipogenesis in subcutaneous adipose tissue from lactating and nonlactating sheep. *Journal of Animal Science* **79**, 445-452.

Nieri, P., Greco, R., Adinolfi, B., Breschi, M.C., Martinotti, E., Nannetti, C. and Podesta, A. (2003) CB1- and CB2-cannabinoid receptor-independent lipolysis induced by WIN 55,212-2 in male rat adipocytes. *Naunyn-Schmiedebergs Archives of Pharmacology* **368**, 352-359.

Noon, L.A., Clark, A.J. and King, P.J. (2004) A peroxisome proliferator-response element in the murine mc2-r promoter regulates its transcriptional activation during differentiation of 3T3-L1 adipocytes. *Journal of Biological Chemistry* **279**, 22803-22808.

Norman, D., Isidori, A.M., Frajese, V., Caprio, M., Chew, S.L., Grossman, A.B., Clark, A.J., Mi-chael Besser, G. and Fabbri, A. (2003) ACTH and alpha-MSH inhibit leptin expression and secretion in 3T3-L1 adipocytes: model for a central-peripheral melanocortin-leptin pathway. *Molecular and Cellular Endocrinology* **200**, 99-109.

Oben, J., Morgan, L., Fletcher, J. and Marks, V. (1991) Effect of the entero-pancreatic hormones, gastric inhibitory polypeptide and glucagon-like polypeptide-1(7-36) amide, on fatty acid synthesis in explants of rat adipose tissue. *Journal of Endocrinology* **130**, 267-272.

Oberkofler, H., Dallinger, G., Liu, Y.M., Hell, E., Krempler, F. and Patsch, W. (1997) Uncoupling protein gene: quantification of expression levels in adipose tissues of obese and non-obese humans. *Journal of Lipid Research* **38**, 2125-2133.

Oelofsen, W. and Ramachandran, J. (1983) Studies of corticotropin receptors on rat adipocytes. *Archives of Biochemistry and Biophysics* **225**, 414-421.

Ogihara, T., Asano, T., Ando, K., Chiba, Y., Sakoda, H., Anai, M., Shojima, N., Ono, H., Onishi, Y., Fujishiro, M., Katagiri, H., Fukushima, Y., Kikuchi, M., Noguchi, N., Aburatani, H., Komuro, I. and Fujita, T. (2002) Angiotensin II-induced insulin resistance is associated with enhanced insulin signaling. *Hypertension* **40**, 872-879.

Okamura, H., Kelly, P.A., Chabot, J.G., Morel, G., Belles-Isles, M. and Heisler, S. (1988) Atrial natriuretic peptide receptors are present in brown adipose tissue. *Biochemical and Biophysical Research Communications* **156**, 1000-1006.

Oldfield, B.J., Giles, M.E., Watson, A., Anderson, C., Colvill, L.M. and McKinley, M.J. (2002) The neurochemical characterisation of hypothalamic pathways projecting polysynaptically to brown adipose tissue in the rat. *Neuroscience* **110**, 515-526.

Oral, E.A., Simha, V., Ruiz, E., Andewelt, A., Premkumar, A., Snell, P., Wagner, A.J., DePaoli, A.M., Reitman, M.L., Taylor, S.I., Gorden, P. and Garg, A. (2002) Leptin-replacement therapy for lipodystrophy. *New England Journal of Medicine* **346**, 570-578.

Ott, V., Fasshauer, M., Dalski, A., Klein, H.H. and Klein, J. (2002a) Direct effects of ciliary neurotrophic factor on brown adipocytes: evidence for a role in peripheral regulation of energy homeostasis. *Journal of Endocrinology* **173**, R1-8.

Ott, V., Fasshauer, M., Dalski, A., Meier, B., Perwitz, N., Klein, H.H., Tschop, M. and Klein, J. (2002b) Direct peripheral effects of ghrelin include suppression of adiponectin expression. *Hormone and Metabolic Research* **34**, 640-645.

Ott, V., Fasshauer, M., Meier, B., Dalski, A., Kraus, D., Gettys, T.W., Perwitz, N. and Klein, J. (2004) Ciliary neurotrophic factor influences endocrine adipocyte function: inhibition of leptin via PI 3-kinase. *Molecular and Cellular Endocrinology* **224**, 21-27.

Pelleymounter, M.A., Cullen, M.J., Baker, M.B., Hecht, R., Winters, D., Boone, T. and Collins, F. (1995) Effects of the obese gene product on body weight regulation in ob/ob mice. *Science* **269**, 540-543.

Penfornis, P., Viengchareun, S., Le Menuet, D., Cluzeaud, F., Zennaro, M.C. and Lombes, M. (2000) The mineralocorticoid receptor mediates aldosterone-induced differentiation of T37i cells into brown adipocytes. American Journal of Physiology. *Endocrinology and Metabolism* **279**, E386-394.

Perea, A., Vinambres, C., Clemente, F., Villanueva-Penacarrillo, M.L. and Valverde, I. (1997) GLP-1 (7-36) amide: effects on glucose transport and metabolism in rat adipose tissue. *Hormone and Metabolic Research* **29**, 417-421.

Pereira-da-Silva, M., Torsoni, M.A., Nourani, H.V., Augusto, V.D., Souza, C.T., Gasparetti, A.L., Carvalheira, J.B., Ventrucci, G., Marcondes, M.C., Cruz-Neto, A.P., Saad, M.J., Boschero, A.C., Carneiro, E.M. and Velloso, L.A. (2003) Hypothalamic melanin-concentrating hormone is induced by cold exposure and participates in the control of energy expenditure in rats. *Endocrinology* **144**, 4831-4840.

Perez, C., Fernandez-Galaz, C., Fernandez-Agullo, T., Arribas, C., Andres, A., Ros, M. and Carrascosa, J.M. (2004) Leptin impairs insulin signaling in rat adipocytes. *Diabetes* **53**, 347-353.

Perry, C.G., Palmer, T., Cleland, S.J., Morton, I.J., Salt, I.P., Petrie, J.R., Gould, G.W. and Connell, J.M. (2003) Decreased insulin sensitivity during dietary sodium restriction is not mediated by effects of angiotensin II on insulin action. *Clin Sci* (Lond) **105**, 187-194.

Pertwee, R.G. and Fernando, S.R. (1996) Evidence for the presence of cannabinoid CB1 receptors in mouse urinary bladder. *British Journal of Pharmacology* **118**, 2053-2058.

Perwitz, N., Sievert, H., Meier, B., Fasshauer, M. and Klein, J. (2005) Cocaine- and amphetamine-related transcript (CART) directly alters adipose tissue thermogenesis, insulin sensitivity, and leptin expression. *Experimental and Clinical Endocrinology and Diabetes* **113**, S21.

Pissios, P. and Maratos-Flier, E. (2003) Melanin-concentrating hormone: from fish skin to skinny mammals. *Trends in Endocrinology and Metabolism* **14**, 243-248.

Pitt, B., Zannad, F., Remme, W.J., Cody, R., Castaigne, A., Perez, A., Palensky, J. and Wittes, J. (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *New England Journal of Medicine* **341**, 709-717.

Pitt, B., Remme, W., Zannad, F., Neaton, J., Martinez, F., Roniker, B., Bittman, R., Hurley, S., Kleiman, J. and Gatlin, M. (2003) Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *New England Journal of Medicine* **348**, 1309-1321.

Porter, J.P., Anderson, J.M., Robison, R.J. and Phillips, A.C. (2003) Effect of central angiotensin II on body weight gain in young rats. *Brain Research* **959**, 20-28.

Porter, J.P. and Potratz, K.R. (2004) Effect of intracerebroventricular angiotensin II on body weight and food intake in adult rats. *Am J Physiol Regul Integr Comp Physiol* **287**, R422-428.

Qi, Y., Takahashi, N., Hileman, S.M., Patel, H.R., Berg, A.H., Pajvani, U.B., Scherer, P.E. and Ahima, R.S. (2004) Adiponectin acts in the brain to decrease body weight. *Nature Medicine* **10**, 524-529.

Ramachandran, J., Farmer, S.W., Liles, S. and Li, C.H. (1976) Comparison of the steroidogenic and melanotropic activities of corticotropin, alpha-melanotropin and analogs with their lipolytic activities in rat and rabbit adipocytes. *Biochimica et Biophysica Acta* **428**, 347-354.

Ramachandran, J. and Lee, V. (1976) Divergent effects of adrenocorticotropin and melanotropin on isolated rat and rabbit adipocytes. *Biochimica et Biophysica Acta* **428**, 339-346.

Ramsay, T.G. (2001) Porcine leptin alters insulin inhibition of lipolysis in porcine adipocytes *in vitro*. *Journal of Animal Science* **79**, 653-657.

Ramsay, T.G. (2003) Porcine leptin inhibits lipogenesis in porcine adipocytes. *Journal of Animal Science* **81**, 3008-3017.

Ranganathan, S., Ciaraldi, T.P., Henry, R.R., Mudaliar, S. and Kern, P.A. (1998) Lack of effect of leptin on glucose transport, lipoprotein lipase, and insulin action in adipose and muscle cells. *Endocrinology* **139**, 2509-2513.

Rice, W., Shannon, J.M., Burton, F. and Fiedeldey, D. (1997) Expression of a brain-type cannabinoid receptor (CB1) in alveolar Type II cells in the lung: regulation by hydrocortisone. *European Journal of Pharmacology* **327**, 227-232.

Richter, W.O. and Schwandt, P. (1985) Peptide hormones and lipolysis in rabbit adipocytes. *Hormone and Metabolic Research* **17**, 127-130.

Rodriguez, V.M., Macarulla, M.T., Echevarria, E. and Portillo, M.P. (2003) Lipolysis induced by leptin in rat adipose tissue from different anatomical locations. *European Journal of Nutrition* **42**, 149-153.

Rohner-Jeanrenaud, F., Craft, L.S., Bridwell, J., Suter, T.M., Tinsley, F.C., Smiley, D.L., Burkhart, D.R., Statnick, M.A., Heiman, M.L., Ravussin, E. and Caro, J.F. (2002) Chronic central infusion of cocaine- and amphetamine-regulated transcript (CART 55-102): effects on body weight homeostasis in lean and high-fat-fed obese rats. *International Journal of Obesity and Related Metabolic Disorders* **26**, 143-149.

Rondinone, C.M., Rodbard, D. and Baker, M.E. (1993) Aldosterone stimulated differentiation of mouse 3T3-L1 cells into adipocytes. *Endocrinology* **132**, 2421-2426.

Rothwell, N.J. and Stock, M.J. (1985a) Thermogenesis and BAT activity in hypophysectomized rats with and without corticotropin replacement. *American Journal of Physiology* **249**, E333-336.

Rothwell, N.J. and Stock, M.J. (1985b) Acute and chronic effects of ACTH on thermogenesis and brown adipose tissue in the rat. *Comparative Biochemistry and Physiology. A: Comparative Physiology* **81**, 99-102.

Rouru, J., Cusin, I., Zakrzewska, K.E., Jeanrenaud, B. and Rohner-Jeanrenaud, F. (1999) Effects of intravenously infused leptin on insulin sensitivity and on the expression of uncoupling proteins in brown adipose tissue. *Endocrinology* **140**, 3688-3692.

Rudman, D. (1975) Effects of choroid plexus peptide IIF on adenylate cyclase and 3',5'-cyclic adenosine monophosphate in adipose tissue. *Journal of Pharmacology and Experimental Therapeutics* **195**, 532-539.

Ruiz-Grande, C., Alarcon, C., Merida, E. and Valverde, I. (1992) Lipolytic action of glucagon-like peptides in isolated rat adipocytes. *Peptides* **13**, 13-16.

Sarraf, P., Frederich, R.C., Turner, E.M., Ma, G., Jaskowiak, N.T., Rivet, D.J., 3rd, Flier, J.S., Lowell, B.B., Fraker, D.L. and Alexander, H.R. (1997) Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. *Journal of Experimental Medicine* **185**, 171-175.

Sartipy, P. and Loskutoff, D.J. (2003) Monocyte chemoattractant protein 1 in obesity and insulin resistance. *Proceedings of the National Academy of Sciences of the United States of America* **100**, 7265-7270.

Sarzani, R., Paci, V.M., Zingaretti, C.M., Pierleoni, C., Cinti, S., Cola, G., Rappelli, A. and Dessi-Fulgheri, P. (1995) Fasting inhibits natriuretic peptides clearance receptor expression in rat adipose tissue. *Journal of Hypertension* **13**, 1241-1246.

Sarzani, R., Dessi-Fulgheri, P., Paci, V.M., Espinosa, E. and Rappelli, A. (1996) Expression of natriuretic peptide receptors in human adipose and other tissues. *Journal of Endocrinological Investigation* **19**, 581-585.

Scarpace, P.J., Matheny, M., Pollock, B.H. and Tumer, N. (1997) Leptin increases uncoupling protein expression and energy expenditure. *American Journal of Physiology* **273**, E226-230.

Scarpace, P.J. and Matheny, M. (1998) Leptin induction of UCP1 gene expression is dependent on sympathetic innervation. *American Journal of Physiology* **275**, E259-264.

Scarpace, P.J., Nicolson, M. and Matheny, M. (1998) UCP2, UCP3 and leptin gene expression: modulation by food restriction and leptin. *Journal of Endocrinology* **159**, 349-357.

Scarpace, P.J., Matheny, M., Moore, R.L. and Kumar, M.V. (2000) Modulation of uncoupling protein 2 and uncoupling protein 3: regulation by denervation, leptin and retinoic acid treatment. *Journal of Endocrinology* **164**, 331-337.

Scarpace, P.J., Matheny, M., Zhang, Y., Shek, E.W., Prima, V., Zolotukhin, S. and Tumer, N. (2002) Leptin-induced leptin resistance reveals separate roles for the anorexic and thermogenic responses in weight maintenance. *Endocrinology* **143**, 3026-3035.

Sengenès, C., Berlan, M., De Glisezinski, I., Lafontan, M. and Galitzky, J. (2000) Natriuretic peptides: a new lipolytic

pathway in human adipocytes. *FASEB Journal* **14**, 1345-1351.

Sengenès, C., Zakaroff-Girard, A., Moulin, A., Berlan, M., Bouloumie, A., Lafontan, M. and Galitzky, J. (2002) Natriuretic peptide-dependent lipolysis in fat cells is a primate specificity. *American Journal Physiology. Regulatory, Integrative and Comparative Physiology* **283**, R257-265.

Shalev, A., Vosmeer, S. and Keller, U. (1997) Absence of short-term effects of glucagon-like peptide-1 and of hyperglycemia on plasma leptin levels in man. *Metabolism: Clinical and Experimental* **46**, 723-725.

Sharma, A.M., Engeli, S. and Pischon, T. (2001) New developments in mechanisms of obesity-induced hypertension: role of adipose tissue. *Current Hypertension Reports* **3**, 152-156.
Sharma, A.M., Janke, J., Gorzelniak, K., Engeli, S. and Luft, F.C. (2002) Angiotensin blockade prevents type 2 diabetes by formation of fat cells. *Hypertension* **40**, 609-611.

Shi, Y. (2004) Beyond skin color: emerging roles of melanin-concentrating hormone in energy homeostasis and other physiological functions. *Peptides* **25**, 1605-1611.

Shimada, M., Tritos, N.A., Lowell, B.B., Flier, J.S. and Maratos-Flier, E. (1998) Mice lacking melanin-concentrating hormone are hypophagic and lean. *Nature* **396**, 670-674.

Shirakura, S., Furugohri, T. and Tokumitsu, Y. (1990) Activation of glucose transport by activatory receptor agonists of adenylate cyclase in rat adipocytes. Comparative Biochemistry and Physiology. *A: Comparative Physiology* **97**, 81-86.

Siegrist-Kaiser, C.A., Pauli, V., Juge-Aubry, C.E., Boss, O., Pernin, A., Chin, W.W., Cusin, I., Rohner-Jeanrenaud, F., Burger, A.G., Zapf, J. and Meier, C.A. (1997) Direct effects of leptin on brown and white adipose tissue. *Journal of Clinical Investigation* **100**, 2858-2864.

Sivitz, W.I., Fink, B.D. and Donohoue, P.A. (1999) Fasting and leptin modulate adipose and mus-cle uncoupling protein: divergent effects between messenger ribonucleic acid and protein expression. *Endocrinology* **140**, 1511-1519.

Skurk, T., Lee, Y.M. and Hauner, H. (2001a) Angiotensin II and its metabolites stimulate PAI-1 protein release from human adipocytes in primary culture. *Hypertension* **37**, 1336-1340.

Skurk, T., Lee, Y.M., Rohrig, K. and Hauner, H. (2001b) Effect of angiotensin peptides on PAI-1 expression and production in human adipocytes. *Hormone and Metabolic Research* **33**, 196-200.

Skurk, T., van Harmelen, V. and Hauner, H. (2004) Angiotensin II stimulates the release of inter-leukin-6 and interleukin-8 from cultured human adipocytes by activation of NF-kappaB. *Arterio-sclerosis, Thrombosis, and Vascular Biology* **24**, 1199-1203.

Sleeman, M.W., Anderson, K.D., Lambert, P.D., Yancopoulos, G.D. and Wiegand, S.J. (2000) The ciliary neurotrophic factor and its receptor, CNTFR alpha. *Pharmaceutica Acta Helvetiae* **74**, 265-272.

Solomon, S.S., Brush, J.S. and Kitabchi, A.E. (1970) Antilipolytic activity of insulin and proinsulin on ACTH and cyclic nucleotide-induced lipolysis in the isolated adipose cell of rat. *Biochimica et Biophysica Acta* **218**, 167-169.
Spiegelman, B.M. and Flier, J.S. (2001) Obesity and the regulation of energy balance. *Cell* **104**, 531-543.

Spranger, J., Kroke, A., Mohlig, M., Bergmann, M.M., Ristow, M., Boeing, H. and Pfeiffer, A.F. (2003) Adiponectin and protection against type 2 diabetes mellitus. *Lancet* **361**, 226-228.

Starich, G.H., Bar, R.S. and Mazzaferri, E.L. (1985) GIP increases insulin receptor affinity and cellular sensitivity in adipocytes. *American Journal of Physiology* **249**, E603-607.

Stricker-Krongrad, A., Dimitrov, T. and Beck, B. (2001) Central and peripheral dysregulation of melanin-concentrating hormone in obese Zucker rats. Brain Research. *Molecular Brain Research* **92**, 43-48.

Strosberg, A.D. (1997) Towards the development and use of human-selective agonists for the pharmacologic treatment of obesity and diabetes. *J Endocrinol* **155**, 221-222.

Sugihara, H., Miyabara, S., Yonemitsu, N. and Ohta, K. (1983) Hormonal sensitivity of brown fat cells of fetal rats in monolayer culture. *Experimental and Clinical Endocrinology* **82**, 309-319.

Sun, Y., Ahmed, S. and Smith, R.G. (2003) Deletion of ghrelin impairs neither growth nor appetite. *Molecular and Cellular Biology* **23**, 7973-7981.

Sun, Y., Wang, P., Zheng, H. and Smith, R.G. (2004) Ghrelin stimulation of growth hormone release and appetite is mediated through the growth hormone secretagogue receptor. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 4679-4684.

Switonska, M.M., Kaczmarek, P., Malendowicz, L.K. and Nowak, K.W. (2002) Orexins and adi-poinsular axis function in the rat. *Regulatory Peptides* **104**, 69-73.

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

Thompson, N.M., Gill, D.A., Davies, R., Loveridge, N., Houston, P.A., Robinson, I.C. and Wells, T. (2004) Ghrelin and des-octanoyl ghrelin promote adipogenesis directly *in vivo* by a mechanism independent of the type 1a growth hormone secretagogue receptor. *Endocrinology* **145**, 234-242.

Tiraby, C. and Langin, D. (2003) Conversion from white to brown adipocytes: a strategy for the control of fat mass? *Trends in Endocrinology and Metabolism* **14**, 439-441.

Torpy, D.J., Bornstein, S.R., Taylor, W., Tauchnitz, R. and Gordon, R.D. (1999) Leptin levels are suppressed in primary aldosteronism. *Hormone and Metabolic Research* **31**, 533-536.

Tozzo, E., Gnudi, L. and Kahn, B.B. (1997) Amelioration of insulin resistance in streptozotocin diabetic mice by transgenic overexpression of GLUT4 driven by an adipose-specific promoter. *Endocrinology* **138**, 1604-1611.

Tritos, N.A., Mastaitis, J.W., Kokkotou, E. and Maratos-Flier, E. (2001) Characterization of melanin concentrating hormone and preproorexin expression in the murine hypothalamus. *Brain Research* **895**, 160-166.

Ueno, N., Dube, M.G., Inui, A., Kalra, P.S. and Kalra, S.P. (2004) Leptin modulates orexigenic effects of ghrelin and attenuates adiponectin and insulin levels and selectively the dark-phase feeding as revealed by central leptin gene therapy. *Endocrinology* **145**, 4176-4184.

Usdin, T.B., Mezey, E., Button, D.C., Brownstein, M.J. and Bonner, T.I. (1993) Gastric inhibitory polypeptide receptor, a member of the secretin-vasoactive intestinal peptide receptor family, is widely distributed in peripheral organs and the brain. *Endocrinology* **133**, 2861-2870.

Valve, R., Heikkinen, S., Rissanen, A., Laakso, M. and Uusitupa, M. (1998) Synergistic effect of polymorphisms in uncoupling protein 1 and beta3-adrenergic receptor genes on basal metabolic rate in obese Finns. *Diabetologia* **41**, 357-361.

Valverde, I., Merida, E., Delgado, E., Trapote, M.A. and Villanueva-Penacarrillo, M.L. (1993) Presence and characterization of glucagon-like peptide-1(7-36) amide receptors in solubilized membranes of rat adipose tissue. *Endocrinology* **132**, 75-79.

Viengchareun, S., Zennaro, M.C., Pascual-Le Tallec, L. and Lombes, M. (2002) Brown adipocytes are novel sites of expression and regulation of adiponectin and resistin. *FEBS Letters* **532**, 345-350.

Villanueva-Penacarrillo, M.L., Marquez, L., Gonzalez, N., Diaz-Miguel, M. and Valverde, I. (2001) Effect of GLP-1 on lipid metabolism in human adipocytes. *Hormone and Metabolic Research* **33**, 73-77.

Walston, J., Silver, K., Bogardus, C., Knowler, W.C., Celi, F.S., Austin, S., Manning, B., Strosberg, A.D., Stern, M.P., Raben, N., Sorkin, J.D., Roth, J. and Shuldiner, A.R. (1995) Time of onset of non-insulin-dependent diabetes mellitus and genetic variation in the beta3-adrenergic-receptor gene. *New England Journal of Medicine* **333**, 343-347.

Wang, C., Billington, C.J., Levine, A.S. and Kotz, C.M. (2000) Effect of CART in the hypothalamic paraventricular nucleus on feeding and uncoupling protein gene expression. *Neuroreport* **11**, 3251-3255.

Wang, J.L., Chinookoswong, N., Scully, S., Qi, M. and Shi, Z.Q. (1999a) Differential effects of leptin in regulation of tissue glucose utilization *in vivo*. *Endocrinology* **140**, 2117-2124.

Wang, M.Y., Lee, Y. and Unger, R.H. (1999b) Novel form of lipolysis induced by leptin. *Journal of Biological Chemistry* **274**, 17541-17544.

Wang, T.J., Larson, M.G., Levy, D., Benjamin, E.J., Leip, E.P., Wilson, P.W. and Vasan, R.S. (2004) Impact of obesity on plasma natriuretic peptide levels. *Circulation* **109**, 594-600.

Wang, Y., Kole, H.K., Montrose-Rafizadeh, C., Perfetti, R., Bernier, M. and Egan, J.M. (1997) Regulation of glucose transporters and hexose uptake in 3T3-L1 adipocytes: glucagon-like peptide-1 and insulin interactions. *Journal of Molecular Endocrinology* **19**, 241-248.

Welt, C.K., Chan, J.L., Bullen, J., Murphy, R., Smith, P., DePaoli, A.M., Karalis, A. and Mantzo-ros, C.S. (2004) Recombinant human leptin in women with hypothalamic amenorrhea. *New England Journal of Medicine* **351**, 987-997.

Westerterp-Plantenga, M.S., Saris, W.H., Hukshorn, C.J. and Campfield, L.A. (2001) Effects of weekly administration of pegylated recombinant human OB protein on appetite profile and energy metabolism in obese men. *American Journal of Clinical Nutrition* **74**, 426-434.

Widen, E., Lehto, M., Kanninen, T., Walston, J., Shuldiner, A.R. and Groop, L.C. (1995) Association of a polymorphism in the beta3-adrenergic-receptor gene with features of the insulin resistance syndrome in Finns. *New England*

Journal of Medicine **333**, 348-352.

Wikberg, J.E. (1999) Melanocortin receptors: perspectives for novel drugs. *European Journal of Pharmacology* **375**, 295-310.

Wilding, J.P. (2002) Neuropeptides and appetite control. *Diabetic Medicine* **19**, 619-627.

Williams, D.L., Bowers, R.R., Bartness, T.J., Kaplan, J.M. and Grill, H.J. (2003) Brainstem mela-nocortin 3/4 receptor stimulation increases uncoupling protein gene expression in brown fat. *Endocrinology* **144**, 4692-4697.

Williams, G., Cai, X.J., Elliott, J.C. and Harrold, J.A. (2004) Anabolic neuropeptides. *Physiology and Behavior* **81**, 211-222.

Wu, X., Motoshima, H., Mahadev, K., Stalker, T.J., Scalia, R. and Goldstein, B.J. (2003) Involvement of AMP-activated protein kinase in glucose uptake stimulated by the globular domain of adiponectin in primary rat adipocytes. *Diabetes* **52**, 1355-1363.

Wu-Wong, J.R., Berg, C.E., Wang, J., Chiou, W.J. and Fissel, B. (1999) Endothelin stimulates glucose uptake and GLUT4 translocation via activation of endothelin ETA receptor in 3T3-L1 adipocytes. *Journal of Biological Chemistry* **274**, 8103-8110.

Yamauchi, T., Kamon, J., Waki, H., Terauchi, Y., Kubota, N., Hara, K., Mori, Y., Ide, T., Mura-kami, K., Tsuboyama-Kasaoka, N., Ezaki, O., Akanuma, Y., Gavrilova, O., Vinson, C., Reitman, M.L., Kagechika, H., Shudo, K., Yoda, M., Nakano, Y., Tobe, K., Nagai, R., Kimura, S., Tomita, M., Froguel, P. and Kadowaki, T. (2001) The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nature Medicine* **7**, 941-946.

Yang, X., Enerback, S. and Smith, U. (2003) Reduced expression of FOXC2 and brown adipogenic genes in human subjects with insulin resistance. *Obesity Research* **11**, 1182-1191.

Yasuda, T., Masaki, T., Kakuma, T. and Yoshimatsu, H. (2003) Centrally administered ghrelin suppresses sympathetic nerve activity in brown adipose tissue of rats. *Neuroscience Letters* **349**, 75-78.

Yip, R.G., Boylan, M.O., Kieffer, T.J. and Wolfe, M.M. (1998) Functional GIP receptors are present on adipocytes. *Endocrinology* **139**, 4004-4007.

Yip, R.G. and Wolfe, M.M. (2000) GIP biology and fat metabolism. *Life Sciences* **66**, 91-103.

Yokota, T., Meka, C.S., Medina, K.L., Igarashi, H., Comp, P.C., Takahashi, M., Nishida, M., Oritani, K., Miyagawa, J., Funahashi, T., Tomiyama, Y., Matsuzawa, Y. and Kincade, P.W. (2002) Paracrine regulation of fat cell formation in bone marrow cultures via adiponectin and prostaglandins. *Journal of Clinical Investigation* **109**, 1303-1310.

Zabeau, L., Lavens, D., Peelman, F., Eyckerman, S., Vandekerckhove, J. and Tavernier, J. (2003) The ins and outs of leptin receptor activation. *FEBS Letters* **546**, 45-50.

Zhang, H.H., Kumar, S., Barnett, A.H. and Eggo, M.C. (1999) Intrinsic site-specific differences in the expression of leptin in human adipocytes and its autocrine effects on glucose uptake. *Journal of Clinical Endocrinology and Metabolism* **84**, 2550-2556.

Zhang, W., Zhao, L., Lin, T.R., Chai, B., Fan, Y., Gantz, I. and Mulholland, M.W. (2004) Inhibition of adipogenesis by ghrelin. *Molecular Biology of the Cell* **15**, 2484-2491.

Zierath, J.R., Frevert, E.U., Ryder, J.W., Berggren, P.O. and Kahn, B.B. (1998) Evidence against a direct effect of leptin on glucose transport in skeletal muscle and adipocytes. *Diabetes* **47**, 1-4.

Zigman, J.M. and Elmquist, J.K. (2003) Minireview: From anorexia to obesity—the yin and yang of body weight control. *Endocrinology* **144**, 3749-3756.

Zimmer, A., Zimmer, A.M., Hohmann, A.G., Herkenham, M. and Bonner, T.I. (1999) Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. *Proceedings of the National Academy of Sciences of the United States of America* **96**, 5780-5785.

Zvonic, S., Cornelius, P., Stewart, W.C., Mynatt, R.L. and Stephens, J.M. (2003) The regulation and activation of ciliary neurotrophic factor signaling proteins in adipocytes. *Journal of Biological Chemistry* **278**, 2228-2235.