Review Article
TheScientificWorldJOURNAL (2007) 7, 666–685
ISSN 1537-744X; DOI 10.1100/tsw.2007.117

TheScientificWorldJOURNAL
www.thescientificworld.com

The Physiology of Obese-Hyperglycemic Mice [*ob/ob* Mice]

Per Lindström

Department of Integrative Medical Biology, Section for Histology and Cell Biology, Umeå University, S-901 87 Umeå, Sweden

E-mail: per.lindstrom@histocel.umu.se

Received December 22, 2006; Accepted April 4, 2007; Published May 29, 2007

This review summarizes key aspects of what has been learned about the physiology of leptin deficiency as it can be observed in obese-hyperglycemic *ob/ob* mice. These mice lack functional leptin. They are grossly overweight and hyperphagic, particularly at young ages, and develop severe insulin resistance. They have been used as a model for obesity and as a rich source of pancreatic islets with high insulin release capacity. The leptin deficiency manifests also with regard to immune function, the cardiovascular system including angiogenesis, supportive tissue function, malignancies, and reproductive function. *ob/ob* Mice are well suited for studies on the interaction between leptin and insulin, and for studies on initial aspects of metabolic disturbances leading to type-2diabetes.

KEYWORDS: obese hyperglycemic, mice, leptin, pancreatic islets, insulin resistance, immunity, and reproduction

INTRODUCTION

The mouse *ob/ob* syndrome was discovered in 1949 in an outbred colony at Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine[1] and was transferred to the already well-characterized C57Bl mice colony that had been established during the 1930s. *Ob/ob* mice (OM) are hyperphagic, obese, hyperinsulinemic, and hyperglycemic[2,3], and they were used as a model for diabetes and obesity. The pancreatic islets are large and contain a high proportion of insulin-producing ß-cells. OM have, therefore, been used as a source of pancreatic islets for studies of ß-cell function. It was soon discovered that OM have a number of other traits in addition to obesity. They are, for example, infertile and have impaired immune functions.

Elegant parabiosis experiments showed that OM lack, but are very sensitive to, a circulating factor produced by their normal siblings[4,5]. By extensive positional cloning experiments, this factor was identified in 1994 by Friedman and coworkers as leptin produced in adipose tissue[6,7]. The *ob/ob* syndrome can be reversed almost completely even in adult animals by exogenous leptin or transfection with the leptin gene[8,9,10]. There are also cases with leptin deficiency in obese humans, but this is uncommon, so OM do not present a good model for the etiology of human obesity[11]. However, the discovery of leptin has opened up a whole new field of studies on regulation of food intake, metabolic

turnover, and obesity. We also have learned a lot more about the interrelationship between metabolism and other functions, such as reproduction and the immune system.

Insight into the physiology of leptin has been achieved through studies in humans and several animal models, including rodents with leptin receptor defects, such as *db/db* mice and *fa/fa* rats[12,13]. This review will focus on observations in OM. In particular, OM with a relatively mild syndrome will be discussed (see under Metabolism below). The cellular mechanisms for the effects of leptin have been the subject of excellent reviews elsewhere[14,15]. The complex neuropeptidergic control of food intake and metabolic rate in the hypothalamus and other parts of the central nervous system (CNS) is under intense investigation, as well as the connection between metabolic and other hormone-regulated functions. There are also many recent reviews on this[16,17,18,19]. Leptin signaling and insulin-leptin-neuropeptidergic interactions will be referred to, but not covered in any detail, in this presentation.

OM are indistinguishable from their lean littermates at birth, but within 2 weeks, they become heavier and develop hyperinsulinemia. These differences are much more pronounced after weaning and overt hyperglycemia is observed during the fourth week. The blood glucose rises to reach a peak after 3–5 months when the mice also have a very high food intake and a rapid growth[20,21,22]. After that, blood glucose values decrease and eventually become nearly normal at old age. Insulin levels peak later[20]. The animals remain insulin resistant, but impaired glucose tolerance and glycosuria after a glucose load is observed mostly in the postweaning period of rapid growth, and this usually becomes normalized when the mice get older[20,23,24,25].

PANCREATIC ISLETS

The islet volume in OM is up to ten times higher than in normal mice[26,27] and insulin-producing ß-cells are by far the most numerous[20,27,28,29]. The islet hyperplasia is probably not caused by a primary abnormality in the islets due to leptin deficiency; it is rather the consequence of an increased demand for insulin. The growth may be triggered by hyperglycemia, but also by other bloodborne factors and is evident from the fourth week[22]. Persistent hyperglycemia indicates that ß-cell function is insufficient despite hyperinsulinemia, but ß-cells from many OM strains have a high capacity to secrete insulin. After an overnight fast, the blood glucose is nearly normalized and OM islets release larger quantities of insulin after fasting when compared with normal mouse islets[30]. Islets from OM also respond adequately to stimulators and inhibitors of insulin release in most experimental conditions[31,32]. They have therefore been used in several hundred papers as a rich source of ß-cells in studies of islet function.

ß-Cells have leptin receptors and leptin inhibits insulin release in most studies[33,34]. This may explain some of the functional differences between ß-cells from OM and normal mice. The ß-cells also become insulin resistant[35,36] and the difference from lean mouse ß-cells can be viewed as direct adaptations to the OM syndrome with leptin deficiency combined with hyperinsulinemia and hyperglycemia. The threshold for glucose-induced insulin release occurs at a lower glucose concentration[30,37]. The mechanisms for this may, in part, be similar to the glucose hypersensitivity observed after prolonged exposure to elevated glucose also in islets from normoglycemic animals, and involve both metabolic and ionic events[38,39]. Insulin resistance is coupled to a reduced phosphatidylinositol 3-kinase (PI3K)–dependent signaling pathway and a reduced PI3K may result in disinhibition of glucose-induced insulin release[36]. Glucose-6-phosphatase activity is higher in islets from OM[40]. ß-Cells from OM are more sensitive to the stimulatory effect of acetylcholine and the inhibitory effect of noradrenalin[41], but there is age dependence for this. Islets from young OM have an increased ß-cell responsiveness to cholinergic stimulation already from 10–12 days of age[42], but the sensitivity to acetylcholine is reduced at old age, whereas the sensitivity to vagal neuropeptides may be increased[43,44]. Islets from OM respond with a larger increase in insulin release within 10 min after stimulation with ACTH 1-39[45]. OM ß-cells have increased activity of uncoupling protein-2 that may reduce insulin release[46], but knockdown of UCP-2 expression had no effect on glucose-induced insulin

release in OM islets[46]. OM islets have a reduced capacity to accumulate cAMP[47,48], but they are more sensitive to a rise in cAMP[48]. One effect of cAMP could be to reduce the inhibitory effect of a rise in UCP-2[49]. OM ß-cells have an increased Na/K-ATPase activity[50] and may be more sensitive to voltage-dependent events[51], but an impaired function of voltage-dependent Ca^{2+} channels[52] and a disturbed pattern of cytoplasmic calcium changes after glucose stimulation has also been reported[53]. They also do not show the same type of cell-specific Ca^{2+} responses that are found in lean mouse islets[54]. There is an excessive firing of cytoplasmic Ca^{2+} transients when OM ß-cells are stimulated with glucagon[55]. Islet amyloid polypeptide is increased in islets from OM[56]. OM islets also have a reduced capacity to increase blood flow to meet metabolic demands[57].

Glucagon levels are high in OM[58]. It was early hypothesized that elevated glucagon secretion contributes to the altered metabolism of OM[59] and immunoneutralization of endogenous glucagon improves metabolic control[60]. There is a correlation between serum glucagon levels and hepatic glucose output in type-2 diabetic patients[61] and reduction of serum glucagon may be a target for diabetes treatment.

One of the features of OM is that they have large pancreatic islets consisting of mostly ß-cells and OM islets have been used in studies of ß-cell proliferation. There is a good correlation between the level of hyperglycemia and islet cell replication in rats[62] and obese-hyperglycemic mice[63], and the morphology of OM islets reaggregated *in vitro* depends on the glucose concentration[64]. ß-Cell growth is probably stimulated by hyperglycemia directly or indirectly. It has been suggested that cells recruited from bone marrow increase the insulin release capacity in OM[65]. It is also possible that duct progenitor cells are involved in the expansion of the ß-cell mass, but mitotic figures have been demonstrated in ß-cells from OM[22,27] and cells within existing islets are presumably the most important sources for islet cell hyperplasia during expansion of the total islet mass[66]. OM have a growth-promoting environment for ß-cells depending on extra pancreatic factors[67,68] and oncogenes stimulate OM ß-cell replication as a sign that they can be manipulated extrinsically[69]. Bloodborne factors involved probably include NPY[70] and GLP-1[22,71], which both stimulate OM ß-cell replication.

METABOLISM

The most obvious characteristic of leptin-deficient OM is that they are grossly overweight and have high food consumption. They are also hyperglycemic, hyperlipidemic, and hyperinsulinemic. They have a disturbed thermoregulation and lowered physical activity. The lower energy expenditure gives OM an increased food efficiency to accumulate fat, and they have been used in many studies of the effects of antiobesity and antidiabetogenic drugs. Both increased food intake and reduced energy expenditure are direct consequences of leptin deficiency. OM are by definition an excellent model of leptin deficiency. They are perfectly suited for studies of the interaction between leptin and insulin on metabolic functions (in mice), but OM have also been used extensively as a more general model for obesity, insulin resistance, and lipotoxicity. The list includes diabetes. OM may be a model for prediabetes, but the insulin release capacity remains high throughout life[72,73]; the hyperglycemia is reduced after 6 months of age[20]. OM develop peripheral neuropathy[74], but the severity of diabetes complications, such as kidney damage, is much lower than in *db/db* mice[75]. The OM is therefore probably not a good model for all aspects of manifest type-2 diabetes. It has also been questioned whether the effect of leptin to increase energy expenditure applies to humans[76].

It was soon recognized that the *ob/ob* syndrome varies considerably depending on the genetic background[77,78]. In this presentation, "OM" refers to 6J or Umeå *ob/ob* mice unless otherwise stated. On a 6J background, hyperglycemia is relatively mild, particularly at old age, and glycosuria is usually not present in the fasting state. On a KsJ or BTBR background, the mice become overtly diabetic with a reduced life expectancy[4,79]. These mice have a higher food intake than OM on a 6J background[80]. One difference between 6J and KsJ OM is that 6J mice have a larger lipogenic capacity in the liver[81], which may render them less susceptible to lipotoxic effects. ß-Cells from OM accumulate fat, but only a

small lipid increase is observed in ß-cells from OM on a 6J background[82], which is in keeping with the better-preserved function. There are also differences between individual mice from the same colony of 6J and Umeå *ob/ob* strains with regard to hyperglycemia and other aspects of a "diabetes-like" condition. This has been used also to select subgroups of animals within the same strain for metabolic studies.

Food intake is enhanced in OM because of leptin deficiency. Leptin suppresses orexigenic neuropeptide Y (NPY) in the hypothalamus and increases anorectic signals[12]. OM have been a model to study the effect of leptin on food intake, but many observations show clearly that other regulatory systems must also be involved. Insulin is a well-known regulator of food intake[17,18], although this has not been studied much in OM. Dopamine agonists[83,84] reduce food intake and almost reverse the metabolic aspects of the syndrome. Serotonin and serotonin uptake inhibitors reduce food intake and lower the hyperglycemia[85,86]. Other substances that affect food intake in OM in the absence of leptin include antiepileptic drugs[87], cannabinoid receptor agonists[88], peroxisome proliferator-activated receptor activators[89,90,91], endotoxin[92], intracerebroventricular noradrenalin and 5-HT[86], and thyroid hormone[93]. It is very likely that many of these agents exert their effects through the same neuropeptidergic systems as leptin.

OM have a lower body temperature than lean mice and a reduced thermogenic response to cold[94,95,96]. Leptin increases energy expenditure through both central and peripheral effects. Studies with leptin treatment of OM[97,98] and NPY knockouts in OM[99] strongly support that perhaps the most important central effect of leptin is to lower NPY release in the hypothalamus. NPY stimulates food intake, but also inhibits brown adipose tissue thermogenesis[100]. There are many signs of abnormal heat production in brown adipose tissue (BAT) and white adipose tissue (WAT) in OM[101,102]. Uncoupling protein-1 is decreased in both BAT and WAT[103]. PPARγ coactivator-1 (PGC-1) is important for cold-induced up-regulation of UCP-1. PGC-1 is low in OM, and leptin up-regulates PGC-1 in BAT and WAT both *in vivo* and *in vitro*[104]. OM have an impaired capacity to increase the level of thyroxin-dependent enzymes in response to cold[105]. Leptin also induces thermogenesis through increased lipid oxidation independently of uncoupling protein[106].

The main signaling pathways for leptin are the JAK/STAT transduction cascade, the mitogen-activated protein kinase (MAPK) cascade, the PI3K, and the 5'-AMP-activated protein kinase (AMPK) pathways[14,15]. There are different isoforms of the leptin receptor. The full-length leptin receptor is required for the JAK/STAT response, and is present in adipose tissue, muscle, liver, and pancreatic islets[14,15,16,17,18,19]. However, in skeletal muscle, the shorter receptor form, which activates PI3K, is predominant[107]. Leptin signaling pathways may interact with insulin signaling at several points including JAKs, PI3K, and MAPK[108]. This interaction between insulin and leptin is complex and tissue dependent[107,108,109,110], but studies in OM clearly indicate that the net effect of leptin is to increase insulin sensitivity[107,111] and that leptin resistance worsens insulin resistance. High caloric intake and absence of leptin can therefore be partly independent causes of insulin resistance in OM. Obese individuals are usually both insulin resistant and leptin resistant. However, the total absence of leptin signaling from the onset of obesity in OM is in sharp contrast to obesity in humans, and the cross-talk between the cellular effects of insulin and leptin is obviously absent.

Insulin resistance in skeletal muscle is probably central for the metabolic disturbances leading to type-2 diabetes and may be caused by intramyocellular lipid accumulation, which reduces muscle glucose uptake and mitochondrial function[111,112]. Most mechanisms thought to be of importance for the development of insulin resistance have also been observed in OM. OM have increased myocellular lipid content in heart[113,114] and skeletal muscle[115]. Insulin binding and IRS-1 activation is reduced[116,117], and OM skeletal muscle cells have an impaired glucose uptake and glycogen synthesis[116,118]. Glucose transporter (GLUT) 4 is the major glucose transporter of muscle and adipose cells and GLUT-4 is regulated by insulin through post-translational events. Adipocyte GLUT-4 is decreased in OM[119], but not the muscle GLUT-4 protein concentration[120]. GLUT-4 in the arcuate nucleus is higher in OM, particularly at the level of the plasma membrane, which indicates a high glucose uptake[121]. Gluconeogenesis is increased in OM[122,123,124] and is not related to fasting to the same extent as in lean mice[125]. The gluconeogenesis in OM also involves mechanisms that contribute very

little in lean mice, e.g., gluconeogenesis from serine[126]. Muscle protein catabolism is enhanced in OM[127]. Mitochondrial genes involved in muscle mitochondrial respiration are up-regulated in diabetics, but only few of those enzymes are up-regulated in OM[128] and oxygen consumption is reduced in OM muscle fibers[129]. An example of the complexity of the interaction between leptin and insulin is that leptin has a direct inhibitory effect on glycogen synthesis in OM soleus muscle[130].

The muscle insulin resistance is not observed in very young mice, but develops after 3–4 weeks[131]. There is also an age dependence for hepatic and myocardial lipid content that parallels blood glucose and body weight, i.e., an increase in young mice followed by a decrease in old mice, although serum insulin levels are increased throughout life[132,133,134]. The rise in lipogenesis occurs earlier than insulin resistance in some studies[135]. The lack of leptin renders OM muscle tissue unresponsive to changes in body weight and exercise[136].

Mechanisms that can contribute to insulin resistance include the rise in inducible nitric oxide synthase in OM muscle and liver cells[137,138], and the increase in glucose flux via the hexosamine pathway in muscle[120]. Leptin has a direct effect *in vitro* on OM skeletal muscle cells to oppose the lipid incorporating effect of insulin. This improves, but does not correct, insulin resistance[139]. Reduced mitochondrial function may lead to intracellular fat accumulation and lipotoxicity. Mitochondria are impaired in OM adipose tissue[140], liver[141], and skeletal muscle[128,142], but also, for example, in macrophages[143]. Increased lipid peroxidation in the vicinity of mitochondria has been implicated in the pathogenesis of lipotoxicity and OM have increased production of hepatocyte reactive oxygen species[144]. Inhibition of lipid peroxidation reduces liver cell damage in OM[145]. Resistin levels may be high in OM and this can also worsen the insulin resistance[146].

Leptin signals through cytokine receptor–like signals including the JAK/STAT pathway and STAT3 is down-regulated in arcuate nucleus of OM[147]. Leptin also increases JAK/STAT signaling in OM in peripheral tissues[148]. The JAK/STAT pathway is under negative-feedback control by suppressors of cytokine signaling (SOCS). Hypothalamic and liver cell SOCS is induced by leptin in OM[149,150], but SOCS-3 mRNA levels are increased also in untreated OM[151]. Because OM are highly leptin sensitive, the latter observation would speaks against SOCSs being important for the development of leptin resistance, but most likely the increase in SOCS is related to insulin resistance.

Another common pathway for leptin and insulin regulation of metabolism is PI3K activation, which regulates nitric oxide synthase and cAMP formation. Both leptin and insulin stimulate PI3K. PI3K activity is reduced in OM[152] and insulin stimulation of PI3K in muscle is almost absent[153]. The low PI3K activity in OM ß-cells has been suggested to explain the reduced effect of insulin to inhibit insulin release[36].

Protein tyrosine phosphatase 1B (PTP1B) is a negative regulator of both leptin and insulin signaling and overexpression of PTP1B causes leptin resistance[154]. PTP1B levels are increased in OM liver cells[155] and OM has frequently been used for the characterization of PTP1B inhibitors[156]. Leptin up-regulates PTP1B expression in OM liver cells[157]. Probably the leptin-induced increases in both SOCS and PTP1B serve to maintain insulin and leptin signaling in balance.

The leptin receptor shows structural and functional homology with receptors for several cytokines that lack intrinsic kinase activity including IL-6. Serum IL-6 is increased in OM[158] and IL-6 has protective effects on OM hepatocytes with up-regulation of PPARα[159]. TNFα reduces insulin receptor activation of IRS-1. This may be linked to disturbance of detergent resistant membrane micro domains in OM through an increase in the ganglioside GM3[160]. Leptin stimulates the release of TNFα and several other cytokines that affect metabolic functions[161]. However, OM have increased levels of TNFα[162] and OM made TNF deficient are less insulin resistant[163]. It is therefore unclear whether leptin deficiency affects the way cytokines can play a role in insulin resistance and other aspects of metabolism.

OM have adrenal hypertrophy and increased secretion of corticosteroids with normal diurnal rhythm[164,165,166]. One consequence of increased glucocorticoids is a diminished muscle glucose uptake[167]. Adrenalectomy reduces blood glucose and weight gain in both young[168] and adult OM[169], and leptin treatment reduced plasma corticosterone levels, probably because of inhibition of corticotropin-releasing factor neurons[167]. OM also have increased serum cholesterol[164,171]. Early

studies reported no hypertriglyceridemia[19], which is consistent with a lipoprotein profile with elevated LDL and HDL, but low hepatic VLDL secretion[172,173,174]. However, most later studies suggest that there is also a modest hypertriglyceridemia[61,174,175].

Both insulin resistance and altered ß-cell function are secondary events to leptin deficiency in OM. The relatively mild "diabetes", despite severe insulin resistance, could speak in favor of a primary ß-cell defect being decisive for the development of type-2 diabetes. On the other hand, insulin resistance is the primary defect in the desert gerbil *Psammomys obesus* model for type-2 diabetes[176]. *P. obesus* and OM share many features in the initial stages including obesity, hyperinsulinemia, and hyperglycemia, but *P. obesus* are also hyperleptinemic and leptin resistant[173]. Both OM and *P. obesus* have an increased ß-cell sensitivity to glucose[177]. ß-Cell number and insulin release capacity is reduced with age in diabetes prone *P. obesus,* whereas islet size increases up to 6 months of age and insulin release is maintained in OM[73]. Islets from old OM show few signs of degeneration[28] and ß-cell replication can resume in old OM if they are again subjected to high glucose[63]. We do not know why the syndrome in OM does not progress to uncompensated diabetes and ß-cell destruction. The "diabetic" components observed in leptin-deficient humans appear to be rather mild[178,179] and the comparison with the desert gerbil indicates that the metabolic consequences of leptin deficiency can be more easily compensated for even with unlimited food intake. It is also evident from other experience in mice that not only leptin deficiency, but also genetic background plays a role because KsJ OM have impaired islet function[4] and increased lipotoxic islet damage[82] when compared with OM on a 6J background.

The OM metabolic condition causes redistribution of fat storage from fat to liver and other nonadipose tissues. This increased uptake and storage of lipids is thought to induce cell damage and apoptosis. OM hepatocytes have been used as a model system to explore mechanisms underlying initial phases of cytolipotoxicity. OM seldom gets severe liver damage. This can be because they have reduced inflammatory responses and reduced connective tissue formation when compared with normal mice. The condition in OM may be linked may be linked to low adiponektin and high TNFα levels or other strain-related distinctions in lipid handling. See Pertusa et al.[177] for review.

IMMUNE SYSTEM

Overnutrition and obesity is coupled to changes in both the innate and the adaptive immune system, and the concept of "obesitis" has been put forward to describe the many similarities between obesity and inflammation[181]. Malnutrition also clearly affects the immune system in a negative way[182]. There are leptin receptors in all cell types of innate and adaptive immunity[183,184] and leptin affects most aspects of the immune system[185]. OM show differences from lean mice with regard to both defense against infection, rejection reactions, and inflammatory reactions[186,187]. Leptin restores the immune function of OM in parallel with metabolic functions. However, also less dramatic improvements of metabolic function, such as after arginine supplementation[188], stimulate immune function.

Leptin is a survival factor for T-cells during maturation in the thymus[189]. Both the number of T-lymphocytes[190] and the thymus and spleen weights[191] are reduced in OM. Leptin stimulates thymic growth[192] and OM do not have the same increase in T-cells as found in obesity induced by a high fat diet[193]. Several T-cell antigens are expressed aberrantly in OM[194] and leptin directly stimulates $CD4^+$ T-cells from OM[195]. T-cells produce leptin, but adipocyte-derived leptin is probably more important for immune regulation[196].

Phagocytotic activity is decreased in OM macrophages and is stimulated by leptin treatment[143,196,197]. Monocyte chemoattractant protein-1 is induced by insulin in adipose tissue and is increased in OM[198]. This may induce fat cell dedifferentiation and the phagocytic function of preadipocytes is reduced in OM[199]. OM also have impaired antigen-presenting cell function[200].

Beneficial effects of the reduced immune response in OM include lower concentrations of mannan-binding lectin, which can increase the risk of inflammatory disease[201], less severe arthritis after immunization[202], and less colitis after induction of intestinal inflammatory response[203]. OM are also

partially protected against *Clostridium* toxin[55] and against concanavalin-A–induced hepatoxicity[204]. They have a delayed pulmonary response to bacterial infection, but are equally susceptible to disease[205,206]. Cardiac damage induced by viral myocarditis is larger in OM than in lean controls, probably due to a defective T-cell response[207].

THE CARDIOVASCULAR SYSTEM

Leptin increases blood pressure, heart rate, and renal excretory function, most likely through an increased sympathetic nerve activity[208,209,210,211,212,213]. Those observations have mostly been done in rats and rabbits, but OM attest to this because OM have a reduced sympathetic nervous system activity[214]. When compared with normal lean mice, both lower[215] and higher[216] arterial pressure has been observed. The reduced SNS activity may also be an important factor for metabolic derangements[76], and OM may not be a model with hypertension coupled to obesity as part of a metabolic syndrome. The long-standing hyperglycemia of OM reduces vascular muscle contraction in response to glucose[217], but caloric restriction lowers blood pressure in OM as in normal mice, showing that this effect is only partly dependent on leptin[216].

The number of muscular arterioles is reduced in leptin-deficient mice[218]. Leptin receptors are present in endothelial cells and leptin induces angiogenesis in OM[219,220], possibly through the up-regulation of endothelial VEGF[221]. Ischemia-induced retinal neovascularization is markedly suppressed in 17-day-old leptin-deficient OM[221] and leptin stimulates retinal neovascularization. OM have impaired endothelial-dependent vasodilatation and this is also reversed by leptin replacement[222].

Leptin stimulates hematopoiesis through leptin receptors on hematopoietic stem cells[223,224,225,226,227]. There is a weak correlation between blood cell number and serum leptin levels in humans[228]. OM have reduced numbers of mononuclear cells[229], but they are polycythemic[230]. The increased number and size of red blood cells may be caused by the hyperinsulinemia[231]. A changed shape and size of red blood cells, and a reduced deformability is observed in OM, coinciding with a period of very high blood glucose[232,233].

Platelet thrombi form slowly and are unstable in *db/db*[234] and OM, and leptin potentiates the aggregation of OM platelets[235]. The fact that platelets have functional leptin receptors raises the possibility that the hyperleptinemia associated with obesity enhances the risk of atherothrombotic complications[236]. Inhibition of leptin reduced the risk of thrombosis in normal mice[237]. OM are protected from experimentally induced atherogenic insult to the vessel wall and this protection is lost after leptin treatment[238]. Plasminogen activator inhibitor-1 (PAI-1) is increased in serum from OM[239]. OM have perivascular fibrosis, which can be coupled to increased PAI-1 and TGFß[240].

Cardiomyopathy with abnormal diastolic left ventricular function is a finding in many diabetic patients[241]. OM has proven to be a good model for the study of this condition. Reduced myocardial efficiency is an early abnormality in OM[242,243] and disturbed OM cardiac myocyte metabolism precedes cardiomyopathy[242]. OM hearts have increased expression of enzymes that stimulate myocyte fatty acid uptake and triglyceride storage. They also have increased oxidative stress related to enzymes involved in contraction[244]. This is paralleled by cardiac diastolic dysfunction[245] and left ventricular hypertrophy, which is completely reversed by leptin treatment[246] or CNTF[247], but not by weight loss alone. There is also considerably increased cardiac apoptosis in OM[248]. However, in comparison with *db/db* mice, the OM have relatively small changes in cardiac muscle lysosomal enzymes involved in cardiomyopathy[249].

OSTEOGENESIS AND CONNECTIVE TISSUE REPAIR

Obesity and increased body mass have been recognized to “protect” from bone loss and the risk of fracture[250,251]. Leptin levels correlate with fat mass and leptin stimulates bone formation, but there are

conflicting data regarding the correlation between serum leptin levels and bone mass and bone formation in humans[252,253,254,255], particularly when the effect of leptin is analyzed independently of fat mass. It has been debated whether the protective effect of increased body weight is related to fat or muscle mass[250,251]. Leptin-deficient OM have lower bone mass in long bones and reduced bone formation when compared with lean mice[256,257], and this could be restored with leptin treatment[256]. The changes in long bones were observed, particularly at young ages[258,259], and could be related to the low muscle mass[254]. Growth plates of OM have a reduced collagen expression and disturbed collagen fibril arrangement, causing the growth plate to be more vulnerable[260].

Leptin-induced signaling was observed in both osteoblasts and chondrocytes, indicating direct peripheral effects of leptin[253,254,261], but several studies in OM point to a central effect of leptin in stimulating bone formation[262,263,264]. However, vertebrate bone mass is increased in OM[259,262]. This may reflect the balance between stimulatory effects of leptin on both bone formation and bone resorption. The expression of cocaine amphetamine regulated transcript (CART) in the CNS is controlled by leptin and nearly abolished in OM. CART signaling may inhibit RANK ligand expression in osteoblasts and thereby inhibit osteoclast differentiation[265]. OM may have increased bone resorption because leptin inhibition of CART signaling is not present[265]. OM also develop abnormal incisor teeth coinciding with reduced food intake and lowering of body weight at 6–8 months[266].

Skin from OM has a low tensile strength and there is impaired wound healing probably because of reduced collagen deposition[267,268]. Leptin restores the wound healing by increasing fibroblast function, but probably only to a small degree by the increased angiogenesis[269,270]. Systemically and topically supplemented leptin improves re-epithelialization in OM[271]. The effect of leptin on keratinocytes is through the STAT-3 pathway[271,272]. There is less hepatic fibrosis in OM after toxic injury or *Schistosoma mansoni* infection, but fibrosis is observed when the animals have been treated with leptin[273]. The hepatic stellate cells that also account for most of the collagen production produce leptin, and TGFß may mediate the effect of leptin[273,274]. Nitric oxide synthesis is important for normal skin repair. Leptin deficiency is accompanied by dysregulated nitric oxide synthesis, which can be restored by leptin treatment[275].

MALIGNANCIES

Leptin stimulates growth and metastasis in several types of malignancies[276,277,278]. It was early recognized that OM have a lower incidence of many types of malignancies including pulmonary and breast cancer[279,280]. One exception was hepatomas that were more prevalent in OM[280]. Some tumor types like melanoma grow faster in OM, but here there is also a resistance to metastasis formation when compared with lean mice[281,282]. The resistance to metastasis is not fully explained, but probably involves reduced angiogenesis as well as reduced tissue turnover because of increased PAI-1.

REPRODUCTION

The physiological role of leptin in reproduction may be to signal an adequate energy supply for reproductive function[283,284]. The leptin deficiency results in a form of hypogonadotropic hypogonadism[285], and both male and female OM are infertile. Leptin restitution restores both puberty and fertility in OM[285,286,287]. Male OM have impaired spermatogenesis and increased germ cell apoptosis[288], but partial restoration of fertility in male OM is sometimes observed when the mice are cross-bred into another genetic background[289] or after food restriction[290]. A number of early[291] and later studies[292] show that fertility can also be restored by the substitution with gonadotropic hormones.

Leptin regulates food intake and body weight through inhibition of hypothalamic NPY orexigenic signals and stimulation of MSH (MC4) and other anorexigenic signals. Central effects of leptin on

reproduction probably involve inhibition of NPY (Y4), but the role of stimulatory neuropeptides is under debate[12,293,294,295]. Recent studies in OM strongly suggest that kisspeptin/GPR54 signaling is important for the central effects of leptin[296,297]. Leptin plays a role in the initiation of puberty in mice, but this effect may be permissive rather than actually triggering the onset of puberty[298].

The OM metabolic condition as such can affect reproductive organs because cytolipotoxicity of endometrial and ovarian follicular cells is seen in OM older than 4 weeks[299,300,301]. However, leptin may have direct peripheral effects since there are leptin receptors in ovary and decidua, in mature oocytes, and in trophoblast cells[302,303]. The peripheral effects of leptin may include sensitizing the follicles to chorionic gonadotropin[304], but leptin can also induce ovulation by activation of ovarian metalloproteinases independently of hypothalamic GnRH[305]. Leptin is not required for pregnancy and parturition in OM once implantation is established[306].

REFERENCES

1. Ingalls, A.M., Dickie, M.M., and Snell, G.D. (1950) Obese, a new mutation in the house mouse. *J. Hered.* **41,** 317–318.
2. Mayer, J., Russel, E., Bates, M.V., and Dickie, M.M. (1953) Metabolic, nutritional and endocrine studies of the hereditary obesity-diabetes syndrome of mice and mechanism of its development. *Metabolism* **2,** 9–21.
3. Garthwaite, T.L., Martinson, D.R., Tseng, L.F., Hagen, T.C., and Menahan, L.A. (1980) A longitudinal hormonal profile of the genetically obese mouse. *Endocrinology* **107,** 671–676.
4. Coleman, D.L. (1978) Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. *Diabetologia* **14,** 141–148.
5. Coleman, D.L. (1973) Effects of parabiosis of obese with diabetes and normal mice. *Diabetologia* **9,** 294–298.
6. Friedman, J.M., Leibel, R.L., Siegel, D.S., Walsh, J., and Bahary, N. (1991) Molecular mapping of the mouse ob mutation. *Genomics* **11,** 1054–1062.
7. Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., and Friedman, J.M.. (1994) Positional cloning of the mouse obese gene and its human homologue. *Nature.* **372,** 425–432.
8. Larcher, F., Del Rio, M., Serrano, F., Segovia, J.C., Ramirez, A., Meana, A., Page, A., Abad, J.L., Gonzalez, M.A., Bueren, J., Bernad, A., and Jorcano, J.L. (2001) A cutaneous gene therapy approach to human leptin deficiencies: correction of the murine ob/ob phenotype using leptin-targeted keratinocyte grafts. *FASEB J.* **15,** 1529–1538.
9. 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.
10. Halaas, J.L., Gajiwala, K.S., Maffei, M., Cohen, S.L., Chait, B.T., Rabinowitz. D., Lallone, R.L., Burley. S.K., and Friedman, J.M. (1995) Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* **269,** 543–546.
11. Clement, K. (2006) Genetics of human obesity. *C. R. Biol.* **329,** 608–622.
12. Chehab, F.F., Qiu, J., and Ogus, S. (2004) The use of animal models to dissect the biology of leptin. *Recent. Prog. Horm. Res*. **59,** 245–266.
13. Unger, R.H. and Orci, L. (2001) Diseases of liporegulation: new perspective on obesity and related disorders. *FASEB J*. **15,** 312–321.
14. Sweeney, G. (2002) Leptin signaling. *Cell Signal.* **14,** 655–663.
15. Frühbeck, G. (2006) Intracellular signalling pathways activated by leptin. *Biochem. J.* **393,** 7–20.
16. Fernandez-Fernandez, R., Martini, A.C., Navarro, V.M., Castellano, J.M., Dieguez, C., Aguilar, E., Pinilla, L., and Tena-Sempere, M. (2006) Novel signals for the integration of energy balance and reproduction. *Mol. Cell. Endocrinol.* **255,** 127–132.
17. Plum, L., Belgardt, B.F., and Bruning, J.C. (2006) Central insulin action in energy and glucose homeostasis. *J. Clin. Invest.* **116,** 1761–1766.
18. Prodi, E. and Obici, S. (2006) Minireview: the brain as a molecular target for diabetic therapy. *Endocrinology* **147,** 2664–2669.
19 Zhang, Y. and Scarpace, P.J. (2006) The role of leptin in leptin resistance and obesity. *Physiol. Behav.* **88,** 249–256.
20. Westman, S. (1968) Development of the obese-hyperglycemic syndrome in mice. *Diabetologia* **4,** 141–149.
21. Edvell, A. and Lindström, P. (1995) Development of insulin secretory function in young obese hyperglycemic mice (Umeå *ob/ob*). *Metabolism* **44,** 906–913.
22. Edvell, A. and Lindström, P. (1999) Initiation of increased pancreatic growth in young normoglycemic mice (Umeå +/?). *Endocrinology* **140,** 778–783.
23. Herberg, L., Major, E., Hennings, U., Grüneklee, D., Freytag, G., and Gries, F.A. (1970) Differences in the development of the obese-hyperglycemic syndrome in obob and NZO mice. *Diabetologia* **6,** 292–299.
24. Danielsson, Å., Hellman, B., and Täljedal, I.-B. (1968) Glucose tolerance in the period preceding the appearance of

the manifest obese-hyperglycemic syndrome in mice. *Acta Physiol. Scand.* **72,** 81–84.
25. Edvell, A. and Lindström, P. (1998) Vagotomy in young obese hyperglycemic mice: effects on syndrome development and islet proliferation. *Am. J. Physiol.* **274,** E1034–E1039.
26. Bleisch, V.R., Mayer, J., and Dickie, M.M. (1952) Familiar diabetes mellitus in mice associated with insulin resistance, obesity, and hyperplasia of the islands of Langerhans. *Am. J. Pathol.* **28**, 369–385.
27. Gepts, W., Christophe, J., and Mayer, J. (1960) Pancreatic islets in mice with the obese-hyperglycemic syndrome: lack of effect of carbutamide. *Diabetes* **9,** 63–69.
28. Westman, S. (1968) The endocrine pancreas of old obese-hyperglycemic mice. *Acta Med. Upsal.* **73,** 81–89.
29. Baetens, D., Stefan, Y., Ravazzola, M., Malaisse-Lagae, F., Coleman, D.L., and Orci, L. (1978) Alteration of islet cell populations in spontaneously diabetic mice. *Diabetes* **27,** 1–7.
30. Lavine, R.L., Voyles, N., Perrino, P.V., and Recant, L. (1977) Functional abnormalities of islets of Langerhans of obese hyperglycemic mouse. *Am. J. Physiol.* **233,** E86–E90.
31. Hahn, H.J., Hellman, B., Lernmark, Å., Sehlin, J., and Täljedal, I.-B. (1974) The pancreatic ß-cell recognition of insulin secretogogues. Influence of neuraminidase treatment on the release of insulin and the islet content of insulin, sialic acid, and cyclic adenosine 3':5'-monophosphate. *J. Biol. Chem.* **249,** 5275–5284.
32. Hellman, B., Idahl, L.-Å., Lernmark, Å., Sehlin, J., and Täljedal, I.-B. (1974) The pancreatic ß-cell recognition of insulin secretagogues. Comparisons of glucose with glyceraldehyde isomers and dihydroxyacetone. *Arch. Biochem. Biophys.* **162,** 448–457.
33. Kieffer, T.J., Heller, R.S., and Habener, J.F. (1996) Leptin receptors expressed on pancreatic ß-cells. *Biochem. Biophys. Res. Commun.* **224,** 522–527.
34. Emilsson, V., Liu, Y.L., Cawthorne, M.A., Morton, N.M., and Davenport, M. (1997) Expression of the functional leptin receptor mRNA in pancreatic islets and direct inhibitory action of leptin on insulin secretion. *Diabetes* **46,** 313–316.
35. Loreti, L., Dunbar, J.C., Chen, S., and Foà, P.P. (1974) The autoregulation of insulin secretion in the isolated pancreas islets of lean (obob) and obese-hyperglycemic (obob) mice. *Diabetologia* **10,** 309–315.
36. Zawalich, W.S., Tesz, G.J., and Zawalich, K.C. (2002) Inhibitors of phosphatidylinositol 3-kinase amplify insulin release from islets of lean but not obese mice. *J. Endocrinol.* **174,** 247–258.
37. Chen, N.G., Tassava, T.M., and Romsos, D.R. (1993) Threshold for glucose-stimulated insulin secretion in pancreatic islets of genetically obese (ob/ob) mice is abnormally low. *J. Nutr.* **123,** 1567–1574.
38. Ling, Z. and Pipeleers, D.G. (1996) Prolonged exposure of human beta cells to elevated glucose levels results in sustained cellular activation leading to a loss of glucose regulation. *J. Clin. Invest.* **98,** 2805–2812.
39. Khaldi, M.Z., Guiot, Y., Gilon, P., Henquin, J.C., and Jonas, J.C. (2004) Increased glucose sensitivity of both triggering and amplifying pathways of insulin secretion in rat islets cultured for 1 wk in high glucose. *Am. J. Physiol. Endocrinol. Metab.* **287,** E207–E217.
40. Khan, A., Hong-Lie, C., and Landau, B.R. (1995) Glucose-6-phosphatase activity in islets from ob/ob and lean mice and the effect of dexamethasone. *Endocrinology* **136,** 1934–1938.
41. Tassava, T.M., Okuda, T., and Romsos, D.R. (1992) Insulin secretion from ob/ob mouse pancreatic islets: effects of neurotransmitters. *Am. J. Physiol.* **262,** E338–E343.
42. Chen, N.G. and Romsos, D.R. (1995) Enhanced sensitivity of pancreatic islets from preobese 2-week-old ob/ob mice to neurohormonal stimulation of insulin secretion. *Endocrinology* **136,** 505–511.
43. Persson-Sjögren, S. and Lindström, P. (2004) Effects of cholinergic m-receptor agonists on insulin release in islets from obese and lean mice of different ages: the importance of bicarbonate. *Pancreas* **29,** 90–99.
44. Persson-Sjögren, S., Forsgren, S., and Lindström, P. (2006) Vasoactive intestinal polypeptide and pituitary adenylate cyclase activating polypeptide: effects on insulin release in isolated mouse islets in relation to metabolic status and age. *Neuropeptides* **40,** 283–290.
45. Bailey, C.J. and Flatt, P.R. (1987) Insulin releasing effects of adrenocorticotropin (ACTH 1-39) and ACTH fragments (1-24 and 18-39) in lean and genetically obese hyperglycaemic (ob/ob) mice. *Int. J. Obes.* **11,** 175–181.
46. Saleh, M.C., Wheeler, M.B., and Chan, C.B. (2006) Endogenous islet uncoupling protein-2 expression and loss of glucose homeostasis in ob/ob mice. *J. Endocrinol.* **190,** 659–667.
47. Black, M.A., Heick, H.M., and Begin-Heick, N. (1988) Abnormal regulation of cAMP accumulation in pancreatic islets of obese mice. *Am. J. Physiol.* **255,** E833–E838.
48. Black, M.A., Heick, H.M., and Begin-Heick, N. (1986) Abnormal regulation of insulin secretion in the genetically obese (ob/ob) mouse. *Biochem. J.* **238,** 863–869.
49. McQuaid, T.S., Saleh, M.C., Joseph, J.W., Gyulkhandanyan, A., Manning-Fox, J.E., MacLellan, J.D., Wheeler, M.B., and Chan, C.B. (2006) cAMP-mediated signaling normalizes glucose-stimulated insulin secretion in uncoupling protein-2 overexpressing ß-cells. *J. Endocrinol.* **190,** 669–680.
50. Elmi, A. (2001) Increased number of Na+/K+ ATPase enzyme units in Ob/Ob-mouse pancreatic islets. *Pancreas* **23,** 113–115.
51. Fournier, L.A., Heick, H.M., and Begin-Heick, N. (1990) The influence of K(+)-induced membrane depolarization on insulin secretion in islets of lean and obese (ob/ob) mice. *Biochem. Cell. Biol.* **68,** 243–248.
52. Black, M.A., Fournier, L.A., Heick, H.M., and Begin-Heick, N. (1988) Different insulin-secretory responses to calcium-channel blockers in islets of lean and obese (ob/ob) mice. *Biochem. J.* **249,** 401–407.

53. Ravier, M.A., Sehlin, J., and Henquin, J.C. (2002) Disorganization of cytoplasmic Ca(2+) oscillations and pulsatile insulin secretion in islets from ob/ob mice. *Diabetologia* **45,** 1154–1163.
54. Gustavsson, N., Larsson-Nyren, G., and Lindström, P. (2006) Cell specificity of the cytoplasmic Ca2+ response to tolbutamide is impaired in ß-cells from hyperglycemic mice. *J. Endocrinol.* **190,** 461–470.
55. Ahmed, M. and Grapengiesser, E. (2001) Pancreatic ß-cells from obese-hyperglycemic mice are characterized by excessive firing of cytoplasmic Ca2+ transients. *Endocrine* **15,** 73–78.
56. Tokuyama, Y., Kanatsuka, A., Yamaguchi, T., Ohsawa, H., Makino, H., Nishimura, M., and Yoshida, S. (1993) Islet amyloid polypeptide/amylin contents in pancreata increase in genetically obese and diabetic mice. *Horm. Metab. Res.* **25,** 289–291.
57. Carlsson, P.O., Andersson, A., and Jansson, L. (1996) Pancreatic islet blood flow in normal and obese-hyperglycemic (ob/ob) mice. *Am. J. Physiol.* **271,** E990–E995.
58. Dubuc, P.U., Mobley, P.W., Mahler, R.J., and Ensinck, J.W. (1977) Immunoreactive glucagon levels in obese-hyperglycemic (ob/ob) mice. *Diabetes* **26,** 841–846.
59. Mayer, J. (1960) The obese hyperglycaemic syndrome of mice as an example of "metabolic" obesity. *Am. J. Clin. Nutr.* **8,** 712–718.
60. Sorensen, H., Brand, C.L., Neschen, S., Holst, J.J., Fosgerau, K., Nishimura, E., and Shulman, G.I. (2006) Immunoneutralization of endogenous glucagon reduces hepatic glucose output and improves long-term glycemic control in diabetic ob/ob mice. *Diabetes* **55,** 2843–2848.
61. Gastaldelli, A., Baldi, S., Pettiti, M., Toschi, E., Camastra, S., Natali, A., Landau, B.R., and Ferrannini, E. (2000) Influence of obesity and type 2 diabetes on gluconeogenesis and glucose output in humans: a quantitative study. *Diabetes* **49,** 1367–1373.
62. Bonner-Weir, S., Deery, D., Leahy, J.L., and Weir, G.C. (1989) Compensatory growth of pancreatic ß-cells in adult rats after short-term glucose infusion. *Diabetes* **38,** 49–53.
63. Andersson, A., Korsgren, O., and Naeser, P. (1989) DNA replication in transplanted and endogenous pancreatic islets of obese-hyperglycemic mice at different stages of the syndrome. *Metabolism* **38,** 974–978.
64. Norlund, R., Norlund, L., and Täljedal, I.-B. (1987) Morphogenetic effects of glucose on mouse islet-cell re-aggregation in culture. *Med. Biol.* **65,** 209–216.
65. Kojima, H., Fujimiya, M., Matsumura, K., Nakahara, T., Hara, M., and Chan, L. (2004) Extrapancreatic insulin-producing cells in multiple organs in diabetes. *Proc. Natl. Acad. Sci. U. S. A.* **101,** 2458–2463.
66. Bock, T., Pakkenberg, B., and Buschard, K. (2003) Increased islet volume but unchanged islet number in ob/ob mice. *Diabetes* **52,** 1716–1722.
67. Tyrberg, B., Ustinov, J., Otonkoski, T., and Andersson, A. (2001) Stimulated endocrine cell proliferation and differentiation in transplanted human pancreatic islets: effects of the ob gene and compensatory growth of the implantation organ. *Diabetes* **50,** 301–307.
68. Flier, S.N., Kulkarni, R.N., and Kahn, C.R. (2001) Evidence for a circulating islet cell growth factor in insulin-resistant states. *Proc. Natl. Acad. Sci. U. S. A.*. **98,** 7475–7480.
69. Welsh, M., Welsh, N., Nilsson, T., Arkhammar, P., Pepinsky, R.B., Steiner, D.F., and Berggren, P.O. (1988) Stimulation of pancreatic islet ß-cell replication by oncogenes. *Proc. Natl. Acad. Sci. U. S. A.*. **85,** 116–120.
70. Cho, Y.R. and Kim, C.W. (2004) Neuropeptide Y promotes ß-cell replication via extracellular signal-regulated kinase activation. *Biochem. Biophys. Res. Commun.* **314,** 773–780.
71. Stoffers, D.A., Kieffer, T.J., Hussain, M.A., Drucker, D.J., Bonner-Weir, S., Habener, J.F., and Egan, J.M. (2000) Insulinotropic glucagon-like peptide 1 agonists stimulate expression of homeodomain protein IDX-1 and increase islet size in mouse pancreas. *Diabetes* **49,** 741–748.
72. Westman, S. (1970) Pathogenic aspects of the obese-hyperglycemic syndrome in mice (genotype *obob*): I. Function of the pancreatic B-cells. *Diabetologia* **6,** 279–283.
73. Tomita, T., Doull, V., Pollock, H.G., and Krizsan, D. (1992) Pancreatic islets of obese hyperglycemic mice (ob/ob). *Pancreas* **7,** 367–375.
74. Drel, V.R., Mashtalir, N., Ilnytska, O., Shin, J., Li, F., Lyzogubov, V.V., and Obrosova, I.G. (2006) The leptin-deficient (ob/ob) mouse: a new animal model of peripheral neuropathy of type 2 diabetes and obesity. *Diabetes* **55,** 3335–3343.
75 Allen, T.J., Cooper, M.E., and Lan, H.Y. (2004) Use of genetic mouse models in the study of diabetic nephropathy. *Curr. Atheroscler. Rep.* **6,** 197–202.
76. Hukshorn, C.J. and Saris, W.H. (2004) Leptin and energy expenditure. *Curr. Opin. Clin. Nutr. Metab. Care.* **7,** 629–633.
77. Mayer, J. and Silides, N. (1953) A quantitative method of determination of the diabetogenic activity of growth hormone preparations. *Endocrinology* **52,** 54–56.
78. Coleman, D.L. and Hummel, K.P. (1973) The influence of genetic background on the expression of the obese *(ob)* gene in the mouse. *Diabetologia* **9,** 287–293.
79. Ranheim, T., Dumke, C., Schueler, K.L., Cartee, G.D., and Attie, A.D. (1997) Interaction between BTBR and c57Bl/6J genomes produces an insulin resistance syndrome in [BTBNR x C57Bl/6J] F1 mice. *Arterioscler. Thromb. Vasc. Biol.* **17,** 3286–3293.
80. Stoehr, J.P., Byers, J.E., Clee, S.M., Lan, H., Boronenkov, O.I.V., Schueler, K.L., Yandell, B.S., and Attie, A.D.

(2004) Identification of major quantitative trait loci controlling body weight variation in *ob/ob* mice. *Diabetes* **53,** 245–249.

81. Clee, S.M., Nadler, S.T., and Attie, A.D. (2005) Genetic and genomic studies of the BTBR ob/ob mouse model of type 2 diabetes. *Am. J. Ther.* **12,** 491–498.
82. Garris, D.R. and Garris, B.L. (2004) Cytochemical analysis of pancreatic islet hypercytolipidemia following diabetes (db/db) and obese (ob/ob) mutation expression: influence of genomic background. *Pathobiology* **71,** 231–240.
83. Cincotta, A.H., Tozzo, E., and Scislowski, P.W. (1997) Bromocriptine/SKF38393 treatment ameliorates obesity and associated metabolic dysfunctions in obese (ob/ob) mice. *Life Sci.* **61,** 951–956.
84. Bina, K.G. and Cincotta, A.H. (2000) Dopaminergic agonists normalize elevated hypothalamic neuropeptide Y and corticotropin-releasing hormone, body weight gain, and hyperglycemia in ob/ob mice. *Neuroendocrinology* **71,** 68–78.
85. Thrybom, T., Rooth, P., and Lindström P. (2001) Effect of serotonin reuptake inhibitor on syndrome development in obese hyperglycemic mice (Umea ob/ob). *Metabolism* **50,** 144–150.
86. Currie, P.J. (1993) Differential effects of NE, CLON, and 5-HT on feeding and macronutrient selection in genetically obese [ob/ob] and lean mice. *Brain Res. Bull.* **32,** 133–142.
87. Lalonde, J., Samson, P., Åoulin, S., Deshaies, Y., and Richard, D. (2004) Additive effects of leptin and topiramate in reducing fat deposition in lean and obese ob/ob mice. *Physiol. Behav.* **80,** 415–420.
88. Zhou, D. and Shearman, L.P. (2004) Voluntary exercise augments acute effects of CB1-receptor inverse agonist on body weight loss in obese and lean mice. *Pharmacol. Biochem. Behav.* **77,** 117–125.
89. Chang, A.Y., Wyse, B.M., Gilchrist, B.J., Peterson, T., and Diani, A.R. (1983) Ciglitazone, a new hypoglycemic agent. I. Studies in ob/ob and db/db mice, diabetic Chinese hamsters, and normal and streptozotocin-diabetic rats. *Diabetes* **32,** 830–838.
90. Hulin, B., Clark, D.A., Goldstein, S.W., McDermott, R.E., Dambek, P.J., Kappeler, W.H., Lamphere, C.H., Lewis, D.M., and Rizzi, J.P. (1992) Novel thiazolidine-2,4-diones as potent euglycemic agents. *J. Med. Chem.* **35,** 1853–1864.
91. Edvardsson, U., von Löwenhielm, H.B., Panfilov, O., Nyström, A.C., Nilsson, F., and Dahllöf, B. (2003) Hepatic protein expression of lean mice and obese diabetic mice treated with peroxisome proliferator-activated receptor activators. *Proteomics* **3,** 468–478.
92. Faggioni, R., Fuller, J., Moser, A., Feingold, K.R., and Grünfeld, C. (1997) LPS-induced anorexia in leptin-deficient [ob/ob] and leptin receptor-deficient [db/db] mice. *Am. J. Physiol.* **273***,* R181–R186.
93. Dubuc, P.U. (1991) Effects of phenotype, feeding condition and cold exposure on thyrotropin and thyroid hormones of obese and lean mice. *Endocr. Regul.* **25,** 171–175.
94. Trayhurn, P., Thurlby, P.L., and James, W.P. (1977) Thermogenic defect in pre-obese ob/ob mice. *Nature.* **266,** 60–62.
95. Trayhurn, P. and James, W.P. (1978) Thermoregulation and non-shivering thermogenesis in the genetically obese (ob/ob) mouse. *Pflügers Arch.* **373,** 189–193.
96. Himms-Hagen, J. (1985) Food restriction increases torpor and improves brown adipose tissue thermogenesis in ob/ob mice. *Am. J. Physiol.* **248,** E531–E539.
97. Stephens, T.W., Basisnki, M., Bristow, P.K., Bue-Valleskey, J.M., Burgett, S.G., Craft. L., Hale, J., Hoffman, J., Hsiung, H.M., Kriauciunas, S., MacKellar, W., Rosteck, P.R., Jr., Schoner, B., Smith, D., Tinsley, F.C., Zhang, X.Y., and Heiman, M. (1995) The role of neuropeptide Y in the antiobesity action of the obese gene product. *Nature* **377,** 530–532.
98. Schwartz, M.W., Baskibn, D.G., Bukowski, T.R., Kujiper, J.L., Foster, D., Lasser, G., Prunkard, D.E., Porte, D., Woods, S.C., Seeley, R.J., and Weigle, D.S. (1996) Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in *ob/ob* mice. *Diabetes* **45,** 531–535.
99. Erickson, J.C., Hollopeter, G., and Palmiter, R.D. (1996) Attenuation of the obesity syndrome of ob/ob mice by the loss of neuropeptide Y. *Science* **274,** 1704–1707.
100. Billington, C.J., Briggs, J.E., Grace, M., and Levine, A.S. (1991) Effects of intracerebroventricular injection of neuropeptide Y on energy metabolism. *Am. J. Physiol.* **260,** R321–R327.
101. Hogan, S. and Himms-Hagen, J. (1981) Abnormal brown adipose tissue in genetically obese mice (ob/ob): effect of thyroxine. *Am. J. Physiol.* **241,** E436–E443.
102. Hansen, E.S and Knudsen, J. (1982) Continuous flow microcalorimetric measurement of heat production in white adipose tissue from obese (ob/ob) mice and their lean littermates. *Biochim. Biophys. Acta.* **30,** 418–424.
103. 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.
104. Kakuma, T., Wang, Z.W., Pan, W., Unger, R.H., and Zhou, Y.T. (2000) Role of leptin in peroxisome proliferators-activated receptor gamma coactivator-1 expression. *Endocrinology* **141,** 4576–4582.
105. Kates, A.L. and Himms-Hagen, J. (1990) Defective regulation of thyroxine 5'-deiodinase in brown adipose tissue of ob/ob mice. *Am. J. Physiol.* **258,** E7–E15.
106. Solinas, G., Summermatter, S., Mainieri, D., Gubler, M., Pirola, L., Wymann, M.P., Rusconi, S., Montani, J.P., Seydoux, J., and Dulloo, A.G. (2004) The direct effect of leptin on skeletal muscle thermogenesis is mediated by substrate cycling between de novo lipogenesis and lipid oxidation. *FEBS Lett.* **577,** 539–544.

107 Dyck, D.J., Heigenhauser, G.J., and Bruce, C.R. (2006) The role of adipokines as regulators of skeletal muscle fatty acid metabolism and insulin sensitivity. *Acta Physiol. (Oxf).* **186,** 5–16.

108. Lulu Strat, A., Kokta, T.A., Dodson, M.V., Gertler, A., Wu, Z., and Hill, R.A. (2005) Early signaling interactions between the insulin and leptin pathways in bovine myogenic cells. *Biochim. Biophys. Acta*. **1744,** 164–175.

109. Brabant, G., Müller, G., Horn, R., Anderwald, C., Roden, M., and Nave, H. (2005) Hepatic leptin signaling in obesity. *FASEB J.* **19,** 1048–1050.

110. Kellerer, M., Lammers, R., Fritsche, A., Strack, V., Machicao, F., Borboni, P., Ullrich, A., and Häring, H.U. (2001) Insulin inhibits leptin receptor signalling in HEK293 cells at the level of janus kinase-2: a potential mechanism for hyperinsulinaemia-associated leptin resistance. *Diabetologia* **44,** 1125–1132;

111. Rattarasarn, C. (2006) Physiological and pathophysiological regulation of regional adipose tissue in the development of insulin resistance and type 2 diabetes. *Acta Physiol. (Oxf).* **186,** 87–101.

112. Petersen, K.F. and Shulman, G.I. (2006) Etiology of insulin resistance. *Am. J. Med.* **119(Suppl 1),** S10–S16.

113. Jolly, S.R., Hron, W.T., Lech, J.J., and Menahan, L.A. (1978) Glycerokinase activity and triacylglycerol content in hearts of genetically obese hyperglycemic (ob/ob) mice. *Horm. Metab. Res.* **10,** 172.

114. Giacomelli, F. and Wiener, J. (1979) Primary myocardial disease in the diabetic mouse. An ultrastructural study. *Lab. Invest.* **40,** 460–473.

115. Almond, R.E. and Enser, M. (1984) A histochemical and morphological study of skeletal muscle from obese hyperglycaemic ob/ob mice. *Diabetologia* **27,** 407–413.

116. Le Marchand-Brustel, Y., Jeanrenaud, B., and Freychet, P. (1978) Insulin binding and effects in isolated soleus muscle of lean and obese mice. *Am. J. Physiol.* **234,** E348–E358.

117. Saad, M.J., Araki, E., Miralpeix, M., Rothenberg, P.L., White, M.F., and Kahn, C.R. (1992) Regulation of insulin receptor substrate-1 in liver and muscle of animal models of insulin resistance. *J. Clin. Invest.* **90,** 1839–1849.

118. Cuendet, G.S., Loten, E.G., Jeanrenaud, B., and Renold, A.E. (1976) Decreased basal, noninsulin-stimulated glucose uptake and metabolism by skeletal soleus muscle isolated from obese-hyperglycemic (ob/ob) mice. *J. Clin. Invest.* **58,** 1078–1088.

119. Gettys, T.W., Watson, P.M., Taylor, I.L., and Collins, S. (1997) RU-486 (Mifepristone) ameliorates diabetes but does not correct deficient beta-adrenergic signalling in adipocytes from mature C57BL/6J-ob/ob mice. *Int. J. Obes. Relat. Metab. Disord.* **21,** 865–873.

120. Buse, M.G., Robinson, K.A., Gettys, T.W., McMahon, E.G., and Gulve, E.A. (1997) Increased activity of the hexosamine synthesis pathway in muscles of insulin-resistant ob/ob mice. *Am. J. Physiol.* **272,** E1080–E1088.

121. Komori, T., Morikawa, Y., Tamura, S., Doi, A., Nanjo, K., and Senba, E. (2005) Subcellular localization of glucose transporter 4 in the hypothalamic arcuate nucleus of ob/ob mice under basal conditions. *Brain Res.* **1049,** 34–42.

122. Seidman, I., Horland, A.A., and Teebor, G.W. (1967) Hepatic glycolytic and gluconeogenic enzymes of the obese hyperglycemic mouse. *Biochim. Biophys. Acta* **146,** 600–603.

123. Lombardo, Y.B. and Menahan, L.A. (1979) Gluconeogenesis in perfused livers of genetically obese-hyperglycemic (ob/ob) mice. *Horm. Metab. Res.* **11,** 9–14.

124. Seidman, I., Horland, A.A., and Teebor, G.W. (1970) Glycolytic and gluconeogenic enzyme activities in the hereditary obese-hyperglycemic syndrome and in acquired obesity. *Diabetologia* **6,** 313–316.

125. Turner, S.M., Linfoot, P.A., Neese, R.A., and Hellerstein, M.K. (2005) Sources of plasma glucose and liver glycogen in fasted ob/ob mice. *Acta Diabetol.* **42,** 187–193.

126. Barglow, K.T. and Cravatt, B.F. (2004) Discovering disease-associated enzymes by proteome reactivity profiling. *Chem. Biol.* **11,** 1523–1531.

127. Trostler, N., Amin, R., and Shafrir, E. (1982) Increased protease activity in muscles of obese- (ob/ob) mice. *Int. J. Obes.* **6,** 557–566.

128. Antonetti, D.A., Reynet, C., and Kahn, C.R. (1995) Increased expression of mitochondrial-encoded genes in skeletal muscle of humans with diabetes mellitus. *J. Clin. Invest.* **95,** 1383–1388.

129. Kaplan, M.L. and Oh, S.S. (1991) Oxygen consumption of muscles from ob/ob and Ay/a strains of obese mice. *Int. J. Obes.* **15,** 809–812.

130. Liu, Y.L., Emilsson, V., and Cawthorne, M.A. (1997) Leptin inhibits glycogen synthesis in the isolated soleus muscle of obese (ob/ob) mice. *FEBS Lett.* **411,** 351–355.

131. Grundleger, M.L., Godbole, V.Y., and Thenen, S.W. (1980) Age-dependent development of insulin resistance of soleus muscle in genetically obese (ob/ob) mice. *Am. J. Physiol.* **239,** E363–E371.

132. Zomozely, C. and Mayer, J. (1959) Endogenous dilution of administered labelled acetate during lipogenesis and cholesterolgenesis in two types of obese mice. *Am. J. Physiol.* **196,** 956–960.

133. Menahan, L.A. (1983) Age-related changes in lipid and carbohydrate metabolism of the genetically obese mouse. *Metabolism.* **32,** 172–178.

134. Lord, J.M. and Atkins, T.W. (1985) Effect of age on hepatocyte and soleus muscle insulin receptor binding in lean and genetically obese diabetic (ob/ob) mice. *Diabetes Res.* **2,** 259–265.

135. Kaplan, M.L. and Leveille, G.A. (1981) Development of lipogenesis and insulin sensitivity in tissues of the ob/ob mouse. *Am. J. Physiol.* **240,** E101–E107.

136. Stickland, N.C., Batt, R.A., Crook, A.R., and Sutton, C.M. (1994) Inability of muscles in the obese mouse (ob/ob) to respond to changes in body weight and activity. *J. Anat.* **184,** 527–533.

137. Sugita, H., Fujimoto, M., Yasukawa, T., Shimizu, N., Sugita, M., Yasuhara, S., Martyn, J.A., and Kaneki, M. (2005) Inducible nitric-oxide synthase and NO donor induce insulin receptor substrate-1 degradation in skeletal muscle cells. *J. Biol. Chem.* **280,** 14203–14211.
138. Fujimoto, M., Shimizu, N., Kunii, K., Martyn, J.A., Ueki, K., and Kaneki, M. (2005) A role for iNOS in fasting hyperglycemia and impaired insulin signaling in the liver of obese diabetic mice. *Diabetes* **54,** 1340–1348.
139. Muoio, D.M., Dohm, G.L., Tapscott, E.B., and Coleman, R.A. (1999) Leptin opposes insulin's effects on fatty acid partitioning in muscles isolated from obese ob/ob mice. *Am. J. Physiol*. **276,** E913–E921.
140. Choo, H.J., Kim, J.H., Kwon, O.B., Lee, C.S., Mun, J.Y., Han, S.S., Yoon, Y.S., Yoon, G., Choi, K.M., and Ko, Y.G. (2006) Mitochondria are impaired in the adipocytes of type 2 diabetic mice. *Diabetologia* **49,** 784–791.
141. Melia, H.P., Andrews, J.F., McBennett, S.M., and Porter, R.K. (1999) Effects of acute leptin administration on the differences in proton leak rate in liver mitochondria from ob/ob mice compared to lean controls. *FEBS Lett.* **458,** 261–264.
142. Liu, Q., Bai, C., Chen, F., Wang, R., MacDonald, T., Gu, M., Zhang, Q., Morsy, M.A., and Caskey, C.T. (1998) Uncoupling protein-3: a muscle-specific gene upregulated by leptin in ob/ob mice. *Gene* **207,** 1–7.
143. Lee, F.Y., Li, Y., Yang, E.K., Yang, S.Q., Lin, H.Z., Trush, M.A., Dannenberg, A.J., and Diehl, A.M. (1999) Phenotypic abnormalities in macrophages from leptin-deficient, obese mice. *Am. J. Physiol.* **276,** C386–C394.
144. Laurent, A., Nicco, C., Tran Van Nhieu, J., Borderie, D., Chereau, C., Conti, F., Jaffray, P., Soubrane, O., Calmus, Y., Weill, B., and Batteux, F. (2004) Pivotal role of superoxide anion and beneficial effect of antioxidant molecules in murine steatohepatitis. *Hepatology* **39,** 1277–1285.
145. de Oliveira, C.P., Stefano, J.T., de Lima, V.M., de Sa, S.V., Simplicio, F.I., de Mello, E.S., Correa-Giannella, M.L., Alves, V.A., Laurindo, F.R., de Oliveira, M.G., Giannella-Neto, D., and Carrilho, F.J. (2006) Hepatic gene expression profile associated with non-alcoholic steatohepatitis protection by S-nitroso-N-acetylcysteine in ob/ob mice. *J. Hepatol.* **45,** 725–733.
146. Qi, Y., Nie, Z., Lee, Y.S., Singhal, N.S., Scherer, P.E., Lazar, M.A., and Ahima, R.S. (2006) Loss of resistin improves glucose homeostasis in leptin deficiency. *Diabetes* **55,** 3083–3090.
147. Håkansson-Ovesjö, M.L., Collin, M., and Meister, B. (2000) Down-regulated STAT3 messenger ribonucleic acid and STAT3 protein in the hypothalamic arcuate nucleus of the obese leptin-deficient (ob/ob) mouse. *Endocrinology* **141,** 3946–3955.
148. Laubner, K., Kieffer, T.J., Lam, N.T., Niu, X., Jakob, F., and Seufert, J. (2005) Inhibition of preproinsulin gene expression by leptin induction of suppressor of cytokine signaling 3 in pancreatic ß–cells. *Diabetes* **54,** 3410–3417.
149. Bjørbaek, C., Elmquist, J.K., Frantz, J.D., Shoelson, S.E., and Flier, J.S. (1998) Identification of SOCS-3 as a potential mediator of central leptin resistance. *Mol. Cell.* **1,** 619–625.
150. Waelput, W., Verhee, A., Broekaert, D., Eyckerman, S., Vandekerckhove, J., Beattie, J.H., and Tavernier, J. (2000) Identification and expression analysis of leptin-regulated immediate early response and late target genes. *Biochem. J.* **348,** 55–61.
151. Emilsson, V., Arch, J.R., de Groot, R.P., Lister, C.A., and Cawthorne, M.A. (1999) Leptin treatment increases suppressors of cytokine signaling in central and peripheral tissues. *FEBS Lett.* **455,** 170–174.
152. Kerouz, N.J., Horsch, D., Pons, S., and Kahn, C.R. (1997) Differential regulation of insulin receptor substrates-1 and -2 (IRS-1 and IRS-2) and phosphatidylinositol 3-kinase isoforms in liver and muscle of the obese diabetic (ob/ob) mouse. *J. Clin. Invest.* **100,** 3164–3172.
153. Folli, F., Saad, M.J., Backer, J.M., and Kahn, C.R. (1993) Regulation of phosphatidylinositol 3-kinase activity in liver and muscle of animal models of insulin-resistant and insulin-deficient diabetes mellitus. *J. Clin. Invest.* **92,** 1787–1794.
154. Lam, N.T., Covey, S.D., Lewis, J.T., Oosman, S., Webber, T., Hsu, E.C., Cheung, A.T., and Kieffer, T.J. (2006) Leptin resistance following over-expression of protein tyrosine phosphatase 1B in liver. *J. Mol. Endocrinol.* **36,** 163–174.
155. Gum, R.J., Gaede, L.L., Koterski, S.L., Heindel, M., Clampit, J.E., Zinker, B.A., Trevillyan, J.M., Ulrich, R.G., Jirousek, M.R., and Rondinone, C.M. (2003) Reduction of protein tyrosine phosphatase 1B increases insulin-dependent signaling in ob/ob mice. *Diabetes* **52,** 21–28.
156. Malamas, M.S., Sredy, J., Gunawan, I., Mihan, B., Sawicki, D.R., Seestaller, L., Sullivan, D., and Flam, B.R. (2000) New azolidinediones as inhibitors of protein tyrosine phosphatase 1B with antihyperglycemic properties. *J. Med. Chem.* **43,** 995–1010.
157. Lam, N.T., Lewis, J.T., Cheung, A.T., Luk, C.T., Tse, J., Wang, J., Bryer-Ash, M., Kolls, J.K., and Kieffer, T.J. (2004) Leptin increases hepatic insulin sensitivity and protein tyrosine phosphatase 1B expression. *Mol. Endocrinol.* **18,** 1333–1345.
158. Harkins, J.M., Moustaid-Moussa, N., Chung, Y.J., Penner, K.M., Pestka, J.J., North, C.M., and Claycombe, K.J. (2004) Expression of interleukin-6 is greater in preadipocytes than in adipocytes of 3T3-L1 cells and C57BL/6J and ob/ob mice. *J. Nutr.* **134,** 2673–2677.
159. Hong, F., Radaeva, S., Pan, H.N., Tian, Z., Veech, R., and Gao, B. (2004) Interleukin 6 alleviates hepatic steatosis and ischemia/reperfusion injury in mice with fatty liver disease. *Hepatology* **40,** 933–941.
160. Inokuchi, J. (2006) Insulin resistance as a membrane microdomain disorder. *Biol. Pharm. Bull.* **29,** 1532–1537.
161. Tilg, H. and Moschen, A.R. (2006) Adipocytokines: mediators linking adipose tissue, inflammation and immunity.

Nat. Rev. Immunol. **6,** 772–783.
162. Yamakawa, T., Tanaka, S., Yamakawa, Y., Kiuchi, Y., Isoda, F., Kawamoto, S., Okuda, K., and Sekihara, H. (1995) Augmented production of tumor necrosis factor-alpha in obese mice. *Clin. Immunol. Immunopathol.* **75,** 51–56.
163. Uysal, K.T., Wiesbrock, S.M., Marino, M.W., and Hotamisligil, G.S. (1997) Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature* **389,** 610–614.
164. Mayer, J. and Jones, K. (1953) Hypercholesterolemia in the hereditary obese-hyperglycemic syndrome of mice and mechanism of its development. *Am. J. Physiol.* **175**, 339–342.
165. Edwardson, J.A. and Hough, C.A. (1975) The pituitary-adrenal system of the genetically obese (ob/ob) mouse. *J. Endocrinol.* **65,** 99–107.
166. Saito, M. and Bray, G.A. (1983) Diurnal rhythm for corticosterone in obese (ob/ob) diabetes (db/db) and gold-thioglucose-induced obesity in mice. *Endocrinology* **113,** 2181–2185.
167. Ohshima, K., Shargill, N.S., Chan, T.M., and Bray, G.A. (1989) Effects of dexamethasone on glucose transport by skeletal muscles of obese (ob/ob) mice. *Int. J. Obes.* **13,** 155–163.
168. Bailey, C.J., Day, C., Bray, G.A., Lipson, L.G., and Flatt, P.R. (1986) Role of adrenal glands in the development of abnormal glucose and insulin homeostasis in genetically obese (ob/ob) mice. *Horm. Metab. Res*. **18,** 357–360.
169. Solomon, J., Bradwin, G., Cocchia, M.A., Coffey, D., Condon, T., Garrity, W., and Grieco, W. (1977) Effects of adrenalectomy on body weight and hyperglycemia in five months old Ob/Ob mice. *Horm. Metab. Res.* **9,** 152–156.
170. Huang, Q., Rivest, R., and Richard, D. (1998) Effects of leptin on corticotrophin-releasing factor (CRF) synthesis and CRF neuron activation in the paraventricular hypothalamic nucleus of obese (ob/ob) mice. *Endocrinology* **139,** 1524–1532.
171. Hahn, P. (1980) Cholesterol metabolism in obese mice. *Can. J. Biochem*. **58,** 1258–1160.
172. Lombardo, Y.B., Hron, W.T., Sobocinski, K.A., and Menahan, L.A. (1984) A metabolic profile of fed and fasting genetically obese mice at 4-5 months of age. *Horm. Metab. Res.* **16(Suppl 1),** 37–42.
173. Camus, M.C., Aubert, R., Bourgeois, F., Herzog, J., Alexiu, A., and Lemonnier, D. (1988) Serum lipoprotein and apolipoprotein profiles of the genetically obese ob/ob mouse. *Biochim. Biophys. Acta* **961,** 53–64.
174. Li, X., Grundy, S.M., and Patel, S.B. (1997) Obesity in db and ob animals leads to impaired hepatic very low density lipoprotein secretion and differential secretion of apolipoprotein B-48 and B-100. *J. Lipid Res.* **38,** 1277–1288.
175. Iizuka, K., Miller, B., and Uyeda, K. (2006) Deficiency of carbohydrate-activated transcription factor ChREBP prevents obesity and improves plasma glucose control in leptin-deficient (ob/ob) mice. *Am. J. Physiol. Endocrinol. Metab.* **291,** E358–E364.
176. Kaiser, N., Nesher, R., Donath, M.Y., Fraenkel, M., Behar, V., Magnan, C., Ktorza, A., Cerasi, E., and Leibowitz, G. (2005) Psammomys obesus, a model for environment-gene interactions in type 2 diabetes. *Diabetes* **54,** S137–S144.
177. Pertusa, J.A., Nesher, R., Kaiser, N., Cerasi, E., Henquin, J.C., and Jonas, J.C. (2002) Increased glucose sensitivity of stimulus-secretion coupling in islets from Psammomys obesus after diet induction of diabetes. *Diabetes* **51,** 2552–2560.
178. Montague, C.T., Farooqi, I.S., Whitehead, J.P., Soos, M.A., Rau, H., Wareham, N.J., Sewter, C.P., Digby, J.E., Mohammed, S.N., Hurst, J.A., Cheetham, C.H., Earley, A.R., Barnett, A.H., Prins, J.B., and O'Rahilly, S. (1997) Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* **387,** 903–908.
179. Farooqi, I.S., Jebb, S.A., Langmack, G., Lawrence, E., Cheetham, C.H., Prentice, A.M., Hughes, I.A., McCamish, M.A., and O'Rahilly, S. (1999) Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N. Engl. J. Med.* **341,** 879–884.
180. Diehl, A.M. (2005) Lessons from animal models of NASH. *Hepatol. Res.* **33,** 138–144.
181. Schmidt, M.I. and Duncan, B.B. (2003) Diabesity. An inflammatory metabolic condition. *Clin. Chem. Lab. Med.* **41,** 1120–1130.
182. Buttgereit, F., Burmester, G.R., and Brand, M.D. (2000) Bioenergetics of immune functions: fundamental and therapeutic aspects. *Immunol. Today* **21,** 192–199.
183. Otero, M., Lago, R., Gomez, R., Dieguez, C., Lago, F., Gomez-Reino, J., and Gualillo, O. (2006) Towards a pro–inflammatory and immunomodulatory emerging role of leptin. *Rheumatology* **45,** 944–950.
184. Matarese, G., Moschos, S., and Mantzoros, C.S. (2005) Leptin in immunology. *J. Immunol.* **174,** 3137–3142.
185. La Cava, A. and Matarese, G. (2004) The weight of leptin in immunity. *Nat. Rev. Immunol.* **4,** 371–379.
186. Sheena, J. and Meade, C.J. (1978) Mice bearing the ob/ob mutation have impaired immunity. *Int. Arch. Allergy Appl. Immunol.* **57,** 263–268.
187. Meade, C.J., Sheena, J., and Mertin, J. (1979) Effects of the obese [ob/ob] genotype on spleen cell immune function. *Int. Arch. Allergy Appl. Immunol.* **58,** 121–127.
188. Barbul, A., Sisto, D.A., Wasserkrug, H.L., Levenson, S.M., Efron, G., and Seifter, E. (1981) Arginine stimulates thymic immune function and ameliorates the obesity and the hyperglycemia of genetically obese mice. *J. Parenter. Enteral Nutr.* **5,** 492–495.
189. Howard, J.K., Lord, G.M., Matarese, G., Vendetti, S., Ghatei, M.A., Ritter, M.A., Lechler, R.I., and Bloom, S.R. (1999) Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in ob/ob mice. *J. Clin Invest.* **104,** 1051–1059.
190. Chandra, R.K. 1980. Cell-mediated immunity in genetically obese C57BL/6J ob/ob mice. *Am. J. Clin. Nutr.* **33,** 13–16.

191. Matarese, G. (2000) Leptin and the immune system: how nutritional status influences the immune response. *Eur. Cytokine Netw.* **11,** 7–14.
192. Hick, R.W., Gruver, A.L., Ventevogel, M.S., Haynes, B.F., and Sempowski, G.D. (2006) Leptin selectively augments thymopoiesis in leptin deficiency and lipopolysaccharide-induced thymic atrophy. *J. Immunol.* **177,** 169–176.
193. Caspar-Bauguil, S., Cousin, B., Andre, M., Nibbelink, M., Galinier, A., Periquet, B., Casteilla, L., and Penicaud, L. (2006) Weight-dependent changes of immune system in adipose tissue: importance of leptin. *Exp. Cell Res.* **312,** 2195–202.
194. Ruter, J., Hoffmann, T., Demuth, H.U., Moschansky, P., Klapp, B.F., and Hildebrandt, M. (2004) Evidence for an interaction between leptin, T cell costimulatory antigens CD28, CTLA-4 and CD26 [dipeptidyl peptidase IV] in BCG-induced immune responses of leptin- and leptin receptor-deficient mice. *Biol. Chem.* **385,** 537–541.
195. Lord, G.M., Matarese, G., Howard, J.K., Baker, R.J., Bloom, S.R., and Lechler, R.I. (1998) Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* **394,** 897–901.
196. Fantuzzi, G., Sennello, J.A., Batra, A., Fedke, I., Lehr, H.A., Zeitz, M., and Siegmund, B. (2005) Defining the role of T cell-derived leptin in the modulation of hepatic or intestinal inflammation in mice. *Clin. Exp. Immunol.* **142,** 31–38.
197. Shirshev, S.V. and Orlova, E.G. (2005) Molecular mechanisms of regulation of functional activity of mononuclear phagocytes by leptin. *Biochemistry [Mosc.]* **70,** 841–847.
198. Sartipy, P. and Loskutoff, D.J. (2003) Monocyte chemoattractant protein 1 in obesity and insulin resistance. *Proc. Natl. Acad. Sci. U. S. A.*. **100,** 7265–7270.
199. Cousin, B., Andre, M., Casteilla, L., and Penicaud, L. (2001) Altered macrophage-like functions of preadipocytes in inflammation and genetic obesity. *J. Cell Physiol.* **186,** 380–386.
200. Macia, L., Delacre, M., Abboud, G., Ouk, T.S., Delanoye, A., Verwaerde, C., Saule, P., and Wolowczuk, I. (2006) Impairment of dendritic cell functionality and steady-state number in obese mice. *J. Immunol.* **177,** 5997–6006.
201. Fernandez-Real, J.M., Straczkowski, M., Vendrell, J., Soriguer, F., Perez Del Pulgar, S., Gallart, L., Lopez-Bermejo, A., Kowalska, I., Manco, M., Cardona, F., Garcia-Gil, M.M., Mingrone, G., Richart, C., Ricart, W., and Zorzano, A. (2006) Protection from inflammatory disease in insulin resistance: the role of mannan-binding lectin. *Diabetologia* **49,** 2402–2411.
202. Busso, N., So, A., Chobaz-Peclat, V., Morard, C., Martinez-Soria, E., Talabot-Ayer, D., and Gabay, C. (2002) Leptin signaling deficiency impairs humoral and cellular immune responses and attenuates experimental arthritis. *J. Immunol.* **168,** 875–882.
203. Siegmund, B., Lehr, H.A., and Fantuzzi, G. (2002) Leptin: a pivotal mediator of intestinal inflammation in mice. *Gastroenterology* **122,** 2011–2025.
204. Sennello, J.A., Fayad, R., Morris, A.M., Eckel, R.H., Asilmaz, E., Montez, J., Friedman, J.M., Dinarello, C.A., and Fantuzzi, G. (2005) Regulation of T cell-mediated hepatic inflammation by adiponectin and leptin *Endocrinology* **146,** 2157–2164.
205. Wieland, C.W., Florquin, S., Chan, E.D., Leemans, J.C., Weijer, S., Verbon, A., Fantuzzi, G., and van der Poll, T. (2005) Pulmonary Mycobacterium tuberculosis infection in leptin-deficient ob/ob mice. *Int. Immunol.* **17,** 1399–1408.
206. Wieland, C.W., Stegenga, M.E., Florquin, S., Fantuzzi, G., and van der Poll, T. (2006) Leptin and host defense against Gram-positive and Gram-negative pneumonia in mice. *Shock* **25,** 414–419.
207. Kanda, T., Takahashi, T., Kudo, S., Takeda, T., Tsugawa, H., and Takekoshi, N. (2004) Leptin deficiency enhances myocardial necrosis and lethality in a murine model of viral myocarditis. *Life Sci.* **75,** 1435–1447.
208. Correia, M.L.G., Morgan, D.A., Sivitz, W.I., Mark, A.L., and Haynes, W.G. (2001) Leptin acts in the central nervous system to produce dose-dependent changes in arterial pressure. *Hypertension* **37,** 936–942.
209. Shek, E.W., Brands, M.W., and Hall, J.E. (1998) Chronic leptin infusion increases arterial pressure. *Hypertension* **31,** 409–414.
210. Haynes, W.G., Morgan, D.A., Walsh, S.A., Mark, A.L., and Sivits, W.I. (1997) Receptor-mediated regional sympathetic nerve activation by leptin. *J. Clin. Invest* **100,** 270–278.
211. Matsumura, K., Abe, I., Tsuchihashi, T., and Fujishima, M. (2000) Central effects of leptin on cardiovascular and neurohormonal responses in conscious rabbits. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **278,** R1314–R1320.
212. Jackson, E.K. and Herzer, W.A. (1999) A comparison of the natriuretic/diuretic effects of rat vs. human leptin in the rat. *Am. J. Physiol. Renal Physiol.* **277,** F761–F765.
213. Modan-Moses, D., Ehrlich, S., Kanety, H., Dagan, O., Pariente, C., Esrahi, N., Lotan, D., Vishne, T., Barzilay, Z., and Paret, G. (2001) Circulating leptin and the perioperative neuroendocrinological stress response after pediatric cardiac surgery. *Crit. Care Med.* **29,** 2377–2382.
214. Young, J.B. and Landsberg, L. (1983) Diminished sympathetic nervous system activity in genetically obese (ob/ob) mouse. *Am. J. Physiol.* **245,** E148–E154.
215. Mark, A.L., Shaffer, R.A., Correia, M.L., Morgan, D.A., Sigmund, C.D., and Haynes, W.G. (1999) Contrasting blood pressure effects of obesity in leptin-deficient ob/ob mice and agouti yellow obese mice. *J. Hypertens.* **17,** 1949–1953.
216. Swoap, S.J. (2001) Altered leptin signaling is sufficient, but not required, for hypotension associated with caloric restriction. *Am. J. Physiol. Heart Circ. Physiol.* **281,** H2473–H2479.
217. Nobe, K., Suzuki, H., Sakai, Y., Nobe, H., Paul, R.J., and Momose, K. (2004) Glucose-dependent enhancement of spontaneous phasic contraction is suppressed in diabetic mouse portal vein: association with diacylglycerol-protein kinase C pathway. *J. Pharmacol. Exp. Ther.* **309,** 1263–1272.

218. Bohlen, H.G. and Niggl, B.A. (1979) Adult microvascular disturbances as a result of juvenile onset diabetes in Db/Db mice. *Blood Vessels* **16,** 269–276.
219. Buoloumie, A., Dresler, H.C.A., Lafontan, M., and Busse, R. (1998) Leptin, the product of the *Ob* gene, promotes angiogenesis. *Circ. Res.* **83,** 1059–1066.
220. Sierra-Honigmann, M.R., Nath, A.K., Murakami, C., Garcia-Cardena, G., Papapetropoulos, A., Sessa, W.C., Madge, L.A., Schechner, J.S., Schwabb, M.B., Polverini, P.J., and Flores-Riveros, J.R. (1998) Biological action of leptin as an angiogenic factor. *Science* **281,** 1683–1686.
221. Suganami, E., Takagi, H., Ohashi, H., Suzuma, K., Suzuma, I., Oh, H., Watanabe, D., Ojima, T., Suganami, T., Fujio, Y., Nakao, K., Ogawa, Y., and Yoshimura, N. (2004) Leptin stimulates ischemia-induced retinal neovascularization: possible role of vascular endothelial growth factor expressed in retinal endothelial cells. *Diabetes* **53,** 2443–2448.
222. Winters, B., Mo, Z., Brooks-Asplund, E., Kim, S., Shoukas, A., Li, D., Nyhan, D., and Berkowitz, D.E. (2000) Reduction of obesity, as induced by leptin, reverses endothelial dysfunction in obese [Lep[ob]] mice. *J. Appl. Physiol.* **89,** 2382–2390.
223. Bennett, B.D., Solar, G.P., Yuan, J.Q., Mathias, J., Thomas, G.R., and Matthews, W. (1996) A role for leptin and its cognate receptor in hematopoiesis. *Curr. Biol.* **6,** 1170–1180.
224. Cioffi, J.A., Shafer, A.W., Zupancic, T.J., Smith-Gbur, J., Mikhail, A., Platika, D., and Snodgrass, H.R. (1996) Novel B219/OB receptor isoforms: possible role of leptin in hematopoiesis and reproduction. *Nat. Med.* **2,** 585–589.
225. Gainsford, T., Willson, T.A., Metcalf, D., Handman, E., McFarlane, C., Ng, A., Nicola, N.A., Alexander, W.S., and Hilton, D.J. (1996) Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. *Proc. Natl. Acad. Sci. U. S. A.*. **93,** 14564–14568.
226. Umemoto, Y., Tsuji, K., Yang, F.C., Ebihara, Y., Kaneko, A., Furukawa, S., and Nakahata, T. (1997) Leptin stimulates the proliferation of murine myelocytic and primitive hematopoietic progenitor cells. *Blood* **90,** 3438–3443.
227. Montoye, T., Piessevaux, J., Lavens, D., Wauman, J., Catteeuw, D., Vandekerckhove, J., Lemmens, I., and Tavernier, J. (2006) Analysis of leptin signalling in hematopoietic cells using an adapted MAPPIT strategy. *FEBS Lett.* **580,** 3301–3307.
228. Laharrague, P., Corberand, J., Penicaud, L., and Casteilla, L. (2000) Relationship of human plasma leptin concentration with blood cell parameters. *Haematologica* **85,** 993–994.
229. Faggioni, R., Jones-Carson, J., Reed, D.A., Dinarello, C.A., Feingold, K.R., Grünfeld, C., and Fantuzzi, G. (2000) Leptin-deficient (ob/ob) mice are protected from T cell-mediated hepatotoxicity: role of tumor necrosis factor alpha and IL-18. *Proc. Natl. Acad. Sci. U. S. A.*. **97,** 2367–2372.
230. Wittmers, L.E., Jr. and Haller, E.W. (1982) The onset and development of polycythaemia in the obese mouse [C57 B1/6J ob/ob]. *J. Comp. Pathol.* **92,** 519–525.
231. Engström, K.G., Grankvist, K., and Täljedal, I.-B. (1990) Insulin-driven erythropoiesis may underlie impairment of erythrocyte deformability in hyperinsulinaemic, hyperglycaemic ob/ob-mice. *Diabetologia* **33,** 127–130.
232. Engström, K.G. and Täljedal, I.-B. (1986) Decreased deformability of erythrocytes in hyperglycaemic non-inbred ob/ob mice. *Diabetologia* **29,** 661–666.
233. Engström, K.G. and Täljedal, I.-B. (1987) Altered shape and size of red blood cells in obese hyperglycaemic mice. *Acta Physiol. Scand.* **130,** 535–543.
234. Rosenblum, W.I., El-Sabban, F., and Loria, R.M. (1981) Platelet aggregation in the cerebral and mesenteric microcirculation of mice with genetically determined diabetes. *Diabetes* **30,** 89–92.
235. Konstantinides, S., Schäfer, K., Koschnick, S., and Loskutoff, D.J. (2001) Leptin-dependent platelet aggregation and arterial thrombosis suggests a mechanism for atherothrombotic disease in obesity. *J. Clin. Invest.* **108,** 1533–1540.
236. Konstantinides, S., Schäfer, K., and Loskutoff, D.J. (2001) The prothrombotic effects of leptin possible implications for the risk of cardiovascular disease in obesity. *Ann. N. Y. Acad. Sci.* **947,** 134–142.
237. Konstantinides, S., Schäfer, K., Neels, J.G., Dellas, C., and Loskutoff, D.J. (2004) Inhibition of endogenous leptin protects mice from arterial and venous thrombosis. *Arterioscler. Thromb. Vasc. Biol.* **24,** 2196–2201.
238. Schäfer, K., Halle, M., Goeschen, C., Dellas, C., Pynn, M., Loskutoff, D.J., and Konstantinides, S. (2004) Leptin promotes vascular remodeling and neointimal growth in mice. *Arterioscler. Thromb. Vasc. Biol.* **26,** 112–117.
239. Samad, F. and Loskutoff, D.J. (1996) Tissue distribution and regulation of plasminogen activator inhibitor-1 in obese mice. *Mol. Med.* **2,** 568–582.
240. Zaman, A.K., Fujii, S., Goto, D., Furumoto, T., Mishima, T., Nakai, Y., Dong, J., Imagawa, S., Sobel, B.E., and Kitabatake, A. (2004) Salutary effects of attenuation of angiotensin II on coronary perivascular fibrosis associated with insulin resistance and obesity. *J. Mol. Cell. Cardiol.* **37,** 525–535.
241. An, D. and Rodrigues, B. (2006) Roles of changes in cardiac metabolism in development of diabetic cardiomyopathy. *Am. J. Physiol. Heart Circ. Physiol.* **291,** H1489–H1506.
242. Buchanan, J., Mazumder, P.K., Hu, P., Chakrabarti, G., Roberts, M.W., Yun, U.J., Cooksey, R.C., Litwin, S.E., and Abel, E.D. (2005) Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinology* **146,** 5341–5349.
243. Dong, F., Zhang, X., Yang, X., Esberg, L.B., Yang, H., Zhang, Z., Culver, B., and Ren, J. (2006) Impaired cardiac contractile function in ventricular myocytes from leptin-deficient ob/ob obese mice. *J. Endocrinol.* **188,** 25–36.
244. Li, S.Y., Yang, X., Ceylan-Isik, A.F., Du, M., Sreejayan, N., and Ren, J. (2006) Cardiac contractile dysfunction in Lep/Lep obesity is accompanied by NADPH oxidase activation, oxidative modification of sarco[endo]plasmic

reticulum Ca2+-ATPase and myosin heavy chain isozyme switch. *Diabetologia* **49,** 1434–1446.
245. Christoffersen, C., Bollano, E., Lindegaard, M.L., Bartels, E.D., Goetze, J.P., Andersen, C.B., and Nielsen, L.B. (2003) Cardiac lipid accumulation associated with diastolic dysfunction in obese mice. *Endocrinology* **144,** 3483–3490.
246. Barouch, L.A., Berkowitz, D.E., Harrison, R.W., O'Donnell, C.P., and Hare, J.M. (2003) Disruption of leptin signaling contributes to cardiac hypertrophy independently of body weight in mice. *Circulation* **108,** 754–759.
247. Barouch, L.A., Gao, D., Chen, L., Miller, K.L., Xu, W., Phan, A.C., Kittleson, M.M., Minhas, K.M., Berkowitz, D.E., Wei, C., and Hare, J.M. (2006) Cardiac myocyte apoptosis is associated with increased DNA damage and decreased survival in murine models of obesity. *Circ. Res.* **98,** 119–124.
248. Raju, S.V., Zheng, M., Schuleri, K.H., Phan, A.C., Bedja, D., Saraiva, R.M., Yiginer, O., Vandegaer, K., Gabrielson, K.L., O'Donnell, C.P., Berkowitz, D.E., Barouch, L.A., and Hare, J.M. (2006) Activation of the cardiac ciliary neurotrophic factor receptor reverses left ventricular hypertrophy in leptin-deficient and leptin-resistant obesity. *Proc. Natl. Acad. Sci. U. S. A.*. **103,** 4222–4227.
249. Skoza, L., Giacomelli, F., and Wiener, J. (1980) Lysosomal enzymes in the heart of the genetically diabetic mouse. *Lab. Invest.* **43,** 443–448.
250. Reid, I.R. (2002) Relationships among body mass, its components, and bone. *Bone* **31,** 547–555.
251. Shapses, S.A. and Riedt, C.S. (2006) Bone, body weight, and weight reduction: what are the concerns? *J. Nutr.* **136,** 1453–1456.
252. Oerter-Klein, K., Larmore, K.K.A., de Lanccey, E., Brown, J.M., Considine, R.V., and Hassink, S.G. (1998) Effect of obesity on estradiol level and its relationship to leptin, bone formation and bone mineral density in children. *J. Clin. Endocrinol. Metab.* **83,** 3469–34775.
253. Cornish, J., Callon, K.E., Bava, U., Lin, C., Naot, D., Hill, B.L., Grey, A.B., Broom, N., Myers, D.E., Nicholson, G.C., and Reid, I.R. (2002) Leptin directly regulates bone cell function in vitro and reduces bone fragility in vivo. *J. Endocrinol.* **175,** 405–415.
254. Maor, G., Rochwerger, M., Segev, Y., and Phillip, M. (2002) Leptin acts as a growth factor on the chondrocytes of skeletal growth centers. *J. Bone Miner. Res.* **17,** 1034–1043.
255. Thomas, T. (2004) The complex effects of leptin on bone metabolism through multiple pathways. *Curr. Opin. Pharmacol.* **4,** 295–300.
256. Hamrick, M.W., Della-Fera, M.A., Choi, Y.H., Pennington, C., Hartzell, D., and Baile, C.A. (2005) Leptin treatment induces loss of bone marrow adipocytes and increases bone formation in leptin-deficient ob/ob mice. *J. Bone Miner. Res.* **20,** 994–1001.
257. Hamrick, M.W., Pennington, C., Newton, D., Xie, D., and Isales, C. (2004) Leptin deficiency produces contrasting phenotypes in bones of the limb and spine. *Bone* **34,** 376–383.
258. Ealey, K.N., Fonseca, D., Archer, M.C., and Ward, W.E. (2006) Bone abnormalities in adolescent leptin-deficient mice. *Regul. Pept.* **136,** 9–13.
259. Baldock, P.A., Allison, S., McDonald, M.M., Sainsbury, A., Enriquez, R.F., Little, D.G., Eisman, J.A., Gardiner, E.M., and Herzog, H. (2006) Hypothalamic regulation of cortical bone mass: opposing activity of Y2 receptor and leptin pathway. *J. Bone Miner. Res.* **21,** 1600–1607.
260. Kishida, Y., Hirao, M., Tamai, N., Nampei, A., Fujimoto, T., Nakase, T., Shimizu, N., Yoshikawa, H., and Myoui, A. (2005) Leptin regulates chondrocyte differentiation and matrix maturation during endochondral ossification. *Bone* **37,** 607–621.
261. Steppan, C.M., Crawford, D.T., Chidsey-Frink, K.L., Ke, H., and Swick, A.G. (2000) Leptin is a potent stimulator of bone growth in ob/ob mice. *Regul. Pept.* **92,** 73–78.
262. Karsenty, G. (2001) Leptin controls bone formation through a hypothalamic relay. *Recent Prog. Horm. Res.* **56,** 401–415.
263. Baldock, P.A., Sainsbury, A., Allison, S., Lin, E.J., Couzens, M., Boey, D., Enriquez, R., During, M., Herzog, H., and Gardiner, E.M. (2005) Hypothalamic control of bone formation: distinct actions of leptin and y2 receptor pathways. *J. Bone Miner. Res.* **20,** 1851–1857.
264. Ducy, P., Amling, M., Takeda, S., Priemel, M., Schilling, A.F., Beil, F.T., Shen, J., Vinson, C., Rueger, J.M., and Karsenty, G. (2000) Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. *Cell* **100,** 197–207.
265. Elefteriou, F., Ahn, J.D., Takeda, S., Starbuck, M., Yang, X., Liu, X., Kondo, H., Richards, W.G., Bannon, T.W., Noda, M., Clement, K., Vaisse, C., and Karsenty, G. (2005) Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature* **434,** 514–520.
266. Batt, R.A. (1992) Abnormal incisor teeth and body weight in the obese mouse [genotype ob/ob]. *Int. J. Obes. Relat. Metab. Disord.* **16,** 29–34.
267. Enser, M. and Avery, N.C. (1984) Mechanical and chemical properties of the skin and its collagen from lean and obese-hyperglycaemic [ob/ob] mice. *Diabetologia* **27,** 44–49.
268. Goodson, W.H., 3rd and Hunt, T.K. (1986) Wound collagen accumulation in obese hyperglycemic mice. *Diabetes* **35,** 491–495.
269. Ring, B.D., Scully, S., Davis, C.R., Baker, M.B., Cullen, M.J., Pelleymounter, M.A., and Danilenko, D.M. (2000) Systemically and topically administered leptin both accelerate wound healing in diabetic ob/ob mice. *Endocrinology*

141, 446–449.
270. Stallmeyer, B., Pfeilschifter, J., and Frank, S. (2001) Systemically and topically supplemented leptin fails to reconstitute a normal angiogenic response during skin repair in diabetic ob/ob mice. *Diabetologia* **44,** 471–479.
271. Frank, S., Stallmeyer, B., Kampfer, H., Kolb, N., and Pfeilschifter, J. (2000) Leptin enhances wound re-epithelialization and constitutes a direct function of leptin in skin repair. *J. Clin. Invest.* **106,** 501–509.
272. Goren, I., Pfeilschifter, J., and Frank, S. (2003) Determination of leptin signaling pathways in human and murine keratinocytes. *Biochem. Biophys. Res. Commun*. **303,** 1080–1085.
273. Potter, J.J., Rennie-Tankesley, L., and Mezey, E. (2003) Influence of leptin in the development of hepatic fibrosis produced in mice by Schistosoma mansoni infection and by chronic carbon tetrachloride administration. *J. Hepatol.* **38,** 281–288.
274. Tang, M., Potter, J.J., and Mezey, E. (2002) Leptin enhances the effect of transforming growth factor ß in increasing type I collagen formation. *Biochem. Biophys. Res. Commun.* **297,** 906–911.
275. Kampfer, H., Pfeilschifter, J., and Frank, S. (2003) Expression and activity of arginase isoenzymes during normal and diabetes-impaired skin repair. *J. Invest. Dermatol.* **121,** 1544–1545.
276. Somasundar, P., Yu, A.K., Vona-Davis, L., and McFadden, D.W. (2003) Differential effects of leptin on cancer in vitro. *J. Surg. Res.* **113,** 50–55.
277. Thompson, C.I., Kreider, J.W., Black, P.L., Schmidt, T.J., and Margules, D.L. (1983) Genetically obese mice: resistance to metastasis of B16 melanoma and enhanced T-lymphocyte mitogenic responses. *Science* **220,** 1183–1185.
278. Black, P.L., Holly, M., Thompson, C.I., and Margules, D.L. (1983) Enhanced tumor resistance and immunocompetence in obese (ob/ob) mice. *Life Sci.* **33(Suppl 1),** 715–718.
279. Vlahakis, G. and Heston, W.E. (1959) Relationships between recessice obesity and induced pulmonary tumours in mice. *J. Hered.* **41,** 317–3189.
280. Heston, W.E. and Vlahakis, G. (1962) Genetic obesity and neoplasia. *J. Natl. Cancer Inst.* **29,** 197–209.
281. Sulkowska, M., Golaszewska, J., Wincewicz, A., Koda, M., Baltaziak, M., and Sulkowski, S. (2006) Leptin--from regulation of fat metabolism to stimulation of breast cancer growth. *Pathol. Oncol. Res.* **12,** 69–72.
282. Somasundar, P., McFadden, D.W., Hileman, S.M., and Vona-Davis, L. (2004) Leptin is a growth factor in cancer. *J Surg Res.* **116,** 337–349.
283. Barash, I.A., Cheung, C.C., Weigle, D.S., Ren, H., Kabigting, E.B., Kuijper, J.L., Clifton, D.K., and Steiner, R.A. (1996) Leptin is a metabolic signal to the reproductive system. *Endocrinology* **137,** 3144–3147.
284. Cunningham, M.J., Clifton, D.K., and Steiner, R.A. (1999) Leptin's actions on the reproductive axis: perspectives and mechanisms. *Biol. Reprod.* **60,** 216–222.
285. Chebab, F.F., Lim, M.E., and Lu, R. (1996) Correction of the sterility defect in homozygous obese female mice treated with leptin. *Nat. Genet.* **12,** 318–320.
286. Mounzih, K., Lu, R., and Chehab, F.F. (1997) Leptin treatment rescues the sterility of genetically obese ob/ob males. *Endocrinology* **138,** 1190–1193.
287. Cleary, M.P., Bergstrom, H.M., Dodge, T.L., Getzin, S.C., Jacobson, M.K., and Phillips, F.C. (2001) Restoration of fertility in young obese [Lep[ob] Lep[ob]] male mice with low dose recombinant mouse leptin treatment. *Int. J. Obes. Relat. Metab. Disord.* **25,** 95–97.
288. Bhat, G.K., Sea, T.L., Olatinwo, M.O., Simorangkir, D., Ford, G.D., Ford, B.D., and Mann, D.R. (2006) Influence of a leptin deficiency on testicular morphology, germ cell apoptosis, and expression levels of apoptosis-related genes in the mouse. *J. Androl.* **27,** 302–310.
289. Ewart-Toland, A., Mounzih, K., Qiu, J., and Chehab, F.F. (1999) Effect of the genetic background on the reproduction of leptin-deficient obese mice. *Endocrinology* **140,** 732–738.
290. Lane, P.W. and Dickie, M.M. (1954) Fertile obese male mice. Relative sterility in obese males corrected by dietary restriction. *J. Hered.* **45,** 56–58.
291. Smithberg, M. and Runner, M.N. (1957) Pregnancy induced in genetically sterile mice. *J. Hered.* **48,** 97–100.
292. Swerdloff, R.S., Batt, R.A., and Bray, G.A. (1976) Reproductive hormone function in the genetically obese [*ob/ob*] mouse. *Endocrinology* **98,** 1359–1364.
293. Sainsbury, A., Schwarzer, C., Couzens, M., Jenkins, A., Oakes, S.R., Ormandy, C.J., and Herzog, H. (2002) Y4 receptor knockout rescues fertility in ob/ob mice. *Genes Dev.* **16,** 1077–1088.
294. Bates, S.H., Stearns, W.H., Dundon, T.A., Schubert, M., Tso, A.W., Wang, Y., Banks, A.S., Lavery, H.J., Haq, A.K., Maratos-Flier, E., Neel, B.G., Schwartz, M.W., and Myers, M.G., Jr. (2003) STAT3 signalling is required for leptin regulation of energy balance but not reproduction. *Nature* **421,** 856–859.
295. Barb, C.R. and Kraeling, R.R. (2004) Role of leptin in the regulation of gonadotropin secretion in farm animals. *Anim. Reprod. Sci.* **82–83,** 155–167.
296. Tena-Sempere M. (2006) KiSS-1 and reproduction: focus on its role in the metabolic regulation of fertility. *Neuroendocrinology* **83,** 275–281.
297. Smith, J.T., Acohido, B.V., Clifton, D.K., and Steiner, R.A. (2006) KiSS-1 neurones are direct targets for leptin in the ob/ob mouse. *J. Neuroendocrinol.* **18,** 298–303.
298. Cheung, C.C., Thornton, J.E., Nurani, S.D., Clifton, D.K., and Steiner, R.A. (2001) A reassessment of leptin's role in triggering the onset of puberty in the rat and mouse. *Neuroendocrinology* **74,** 12–21.
299. Garris, D.R. and Garris, B.L. (2004) Cytolipotoxicity-induced involution of the female reproductive tract following

expression of obese [ob/ob] and diabetes [db/db] genotype mutations: progressive, hyperlipidemic transformation into adipocytic tissues. *Reprod. Toxicol.* **18,** 81–91.

300. Garris, D.R. and Garris, B.L. (2004) Genomic modulation of diabetes [db/db] and obese [ob/ob] mutation-induced hypercytolipidemia: cytochemical basis of female reproductive tract involution. *Cell Tissue Res.* **316,** 233–241.
301. Garris, D.R. (2004) Ovarian hypercytolipidemia induced by obese [ob/ob] and diabetes [db/db] mutations: basis of female reproductive tract involution II. *Tissue Cell.* **36,** 157–169.
302. Gonzalez, R.R., Simon, C., Caballero-Campo, P., Norman, R., Chardonnens, D., Devoto, L., and Bischof, P. (2000) Leptin and reproduction. *Hum. Reprod. Update* **6,** 290–300.
303. Zamorano, P.L., Mahesh, V.B., De Sevilla, L.M., Chorich, L.P., Bhat, G.K., and Brann, D.W. (1997) Expression and localization of the leptin receptor in endocrine and neuroendocrine tissues of the rat. *Neuroendocrinology* **65,** 223–228.
304. Olatinwo, M.O., Bhat, G.K., Stah, C.D., and Mann, D.R. (2005) Impact of gonadotropin administration on folliculogenesis in prepubertal ob/ob mice. *Mol. Cell. Endocrinol.* **245,** 121–127.
305. Barkan, D., Hurgin, V., Dekel, N., Amsterdam, A., and Rubinstein, M. (2005) Leptin induces ovulation in GnRH-deficient mice. *FASEB J.* **19,** 133–135.
306. Malik, N.M., Carter, N.D., Murray, J.F., Scaramuzzi, R.J., Wilson, C.A., and Stock, M.J. (2001) Leptin requirement for conception, implantation, and gestation in the mouse. *Endocrinology* **142,** 5198–5202.

This article should be cited as follows:

Lindström, P. (2007) The physiology of obese-hyperglycemic mice [*ob/ob* mice]. *TheScientificWorldJOURNAL* **7**, 666–685. DOI 10.1100/tsw.2007.117.