Sex Steroids Regulation of Appetitive Behavior

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Abstract: Appetite is the desire to satisfy the need to consume food, felt as hunger. It is regulated by the balance of food intake and energy expenditure via signals between the brain, the digestive tract and the adipose tissue. Males and females vary in terms of eating behavior as well as the way the body fat is stored. Energy balance and body fat distribution are part of the sexual dimorphism in many mammalian species including human beings. These sex dissimilarities could be related to the different sex steroid hormone profile in each sex. Gonadal steroid hormones play an important role in the regulation of food intake and energy homeostasis. Human epidemiological and experimental animal studies have shown that estradiol has a key role in the control of food intake and energy balance. Estradiol has long been known to inhibit feeding in animals. There are important changes in food intake patterns during the estrous cycle, with a reduction of food intake around the time of ovulation, when estradiol presents its highest levels. Men have less total fat and more central fat distribution which carries a much greater risk for metabolic disorders while women have more total fat and more gluteal/femoral subcutaneous fat distribution. Men and postmenopausal women accumulate more fat in the intra-abdominal depot. This review is focused on the mechanism by which sex steroids affect feeding behavior and fat distribution.

Keywords: Gonadal steroid, appetite, food intake, estradiol, leptin, insulin.

THE MODULATION OF EATING BY SEX HORMONES

Appetite is defined as the desire to satisfy the need to consume food, felt as hunger. Appetite exists in all higher life-forms and serves to regulate adequate energy intake to maintain metabolic needs. It is regulated by a complex physiological system that balances food intake and energy expenditure via close communication of afferent and efferent signals between the brain, the digestive tract and the adipose tissue.

When a meal is ingested, satiety hormones contribute to a digestion process and a feeling of fullness. Central circuits in the brain integrate satiety signals and signals of long term energy status to produce a coordinated response to the change in nutritional status [1, 2].

Body weight is stable when food intake and energy expenditure are in equilibrium. The hypothalamus integrates signals from central and peripheral pathways to play an important role in appetite regulation [3], and energy homeostasis is controlled by the adipose tissue, pancreas liver, skeletal muscle, endocrine system, and the gastrointestinal tract [1] that provide afferent input to regulate central circuits in the hypothalamus and brain stem to produce a negative or positive effect on energy balance.

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The arcuate nucleus of the hypothalamus integrates signals by altering the relative activity of neurons expressing neuropeptide Y (NPY), Agouti-related protein (AgRP) and the anorexigenic peptides, melanocortin (MSH) and cocaine-amphetamine-regulated transcript (CART). These neuropeptides project to downstream nuclei and modulate the release of further anorectic or orexigenic peptides which under normal circunstances adjust energy intake and expenditure to maintain a stable body weight [4]. While these signals depend on circuits in the hypothalamus, brain stem, and limbic system to modulate neuropeptide release and hence food intake and energy expenditure [4, 5], peripheral signals are driven from adipose tissue (leptin and adiponectin), pancreas (insulin, pancreatic polypeptide PP and glucagon), and gastrointestinal tract (cholecystokinin CCK, peptide YY, glucagon-like peptide-1 GLP-1, oxyntomodulin OXM and ghrelin). These peripheral signals cross the blood-brain barrier and act on brain regions such as the hypothalamus and brain stem.

Gonadal steroid hormones, such as androgens, estrogens and progestins, are well known for their regulation of sexual development and reproductive functions [6, 7].

Sex steroid hormones regulate the Hypothalamus-Pituitary-Gonadal axis by positive and negative feedback actions on receptors at the hypothalamus and pituitary levels but they also play an important role in diverse biological actions (in non-reproductive tissues) non related to their reproductive functions [8].

Obesity represents an ever increasing epidemic in developing and developed countries that causes adverse metabolic problems with important gender differences in the

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prevalence of these metabolic diseases. These sex dissimilarities could be related to the different sex hormone profile in men and women. Sex hormones act on regions of the central nervous system (CNS) involved in the regulation of food intake and energy homeostasis. The expression of sex steroid hormone receptors such as estrogen and androgen receptors has been found in certain neurons of the appetite complexes [9].

Sex steroid hormones have many actions that affect body weight and adiposity independent of eating, including effects on energy expenditure, gastrointestinal function, metabolism, growth and body composition. The mechanisms underlying these effects and their relations to eating are not well understood [8].

Human epidemiological and experimental animal studies have shown that estradiol has a key role in control of food intake and energy balance. In postmenopausal women, when estradiol levels are lower in comparison with a regular cycling woman, the incidence of obesity increases [10], and in female rats the food intake and body weight increases after ovariectomy. Besides the action of estrogens in appetite by regulation of hormones from adipose tissue and pancreas such as leptin, adiponectin and insulin, estrogen reduces food intake and body weight acting directly in the hypothalamus [11].

HORMONAL PERIPHERAL SIGNALS OF FOOD INTAKE

Leptin

Leptin is a 16 kD hormone with 167 aminoacids produced and secreted in a variety of tissues, predominantly by adipocytes [12], that regulates food intake and energy expenditure and has many functions related to growth and development [12, 13]. One of its major functions is to act on hypothalamic arcuate neurons to inhibit food intake by stimulating secretion of the anorexogenic neuropeptides pro-opiomelanocortin (POMC) and CART and thereby inhibits appetitive drive through the interaction with its receptor (Ob-R) which is a member of the cytokine receptor family and has a single trans-membrane domain [14], that presents multiple isoforms resulted from alternative mRNA splicing and post-translational processing [15]. There are three classes of Ob-R: long, short and secreted.

During development leptin plays a major role in organizing the detailed interconnections among the various hypothalamic nuclei involved in appetite. Several studies in rodents have demonstrated a surge of leptin around postnatal days 10 to 14 [16-18]. This surge has been correlated with maturation of the central nervous mechanisms that regulate appetite in later life. Leptin also appears to play a key role in programming the structural and functional development of hypothalamic orexigenic and anorexigenic centers in the early postnatal period, associated with developmental programming of appetitive centers and thought to have an important role in regulating later life leptin sensitivity. Developmental programming is the response to a specific challenge in a critical developmental time window that alters the developmental path with persistent effects. Several studies indicate that the timing and trajectory of the postnatal leptin surge in rodents is critical to the development of obesity in later life [18,19], to our knowledge nobody has reported sexual dimorphism in the postnatal leptin peak..

Circulating levels of leptin correlate positively with the amount of fat stored [20]. Serum leptin concentrations are higher in neonates than adults [21,22] despite the presence of a lower proportion of body fat immediately after birth [22]. Research accomplished in our lab could find no proof that pup serum leptin inhibits milk appetite during the neonatal period, we also found evidence that pup adipose tissue may not be the only neonatal source of leptin in pup serum [18].

Leptin resistance is a result of obesity, but a lack of sensitivity to circulating leptin also contributes to gain body fat and weight. Leptin role is more important in periods of starvation than in times of abundance, during hunger times low leptin levels affects body weight while during obesity high leptin levels have lower effects in decreasing body weight [4].

There is a complex interaction between sex steroids and leptin effects on body weight. The decrease of female sex steroid levels is linked to a significant increase in body weight and food intake, which seems to be related to an impairment of the central actions of leptin [23, 24].

Different studies have shown that sex steroid hormones directly or indirectly regulate leptin production and secretion by adipose cells. Estrogens administration to ovariectomized rats decreases food intake and body weight; it has been suggested that this effect is related to the ability of estrogens to positive regulate leptin gene expression [24].

Various steroid hormones regulate leptin mRNA and protein expression. In rat models the influence of androgenic and estrogenic status on the leptin gene expression has been studied in isolated adipocytes, the results have shown that androgens and estrogens modulate both *in vivo* and *in vitro* leptin gene expression in various white adipose tissues [25]. Androgens have a negative effect and in contrast estrogens a positive effect on leptin expression. These modulation effects are direct, mediated by the adipocyte androgen and estrogen nuclear receptors and affect the leptin gene transcription [25].

Insulin

Insulin is a major metabolic hormone produced by the pancreas and it was the first adiposity signal to be described [26].

Insulin enters into the brain via saturable receptor-mediator uptake across the blood brain barrier at levels proportional to circulating insulin concentrations [27] and acts as an anorexigenic signal, decreasing food intake and body weight. Insulin positively correlated with long-term energy balance. Insulin secretion increases immediately after a meal [28] and its concentrations in blood depend on glucose, body fat storages and distribution, with visceral fat being a key determinant [29].

Insulin signaling involves a cascade of events initiated by insulin binding to its receptor, the insulin receptor is composed of an extracellular α-subunit which binds insulin

followed by receptor autophosphorylation, and an intracellular β-subunit which transduces the signal and has intrinsic tyrosine kinase activity, which results in tyrosine phosphorylation of insulin receptor substrates (IRS) [30, 31], including IRS-1 and IRS-2 identified in neurons [32, 33]. The insulin receptor exists as two splice variants resulting in subtype A, with higher affinity for insulin and more widespread expression, and subtype B with lower affinity and expression in classical insulin responsive tissues such as fat, muscle and liver [32, 33]. Insulin receptors are widely distributed in the brain, particularly in hypothalamic nuclei involved in food intake [34, 35] with the highest concentrations found in the olfactory bulb, hippocampus, cerebral cortex and the arcuate nucleus in the hypothalamus [36].

Insulin is secreted from pancreatic β-cell and decreases blood glucose by promoting glucose uptake by muscle and adipocytes, as well as preventing the formation of glucose by the liver. The ERα and ERβ have been both involved in energy balance, fat and glucose metabolism in hypothalamic neurons, liver, adipose tissue, muscle and the endocrine pancreas, however, data have shown that ERα has a major action. ERα and ERβ as well as membrane estrogen receptors are involved in the regulation of pancreatic β-cell function and hypothalamic neurons [37]. ERα knockout [38] as well as aromatase knockout mice [39] are obese and insulin resistant probably due to lack of estrogen actions [40].

Predisposition to impaire glucose tolerance and insulin resistance are present in ovariectomyzed rats [41] and menopausal women [42], in both conditions estrogen levels are low. This predisposition decreases with estrogen replacement, for both situations [43]. It has also been reported that estrogen function deficiency in men, due to absence of ERα or aromatase, results in impaired glucose metabolism [44].

Changes in blood estrogen levels occur during pregnancy as well as during the menstrual cycle in humans or the estrous cycle in rodents. In each physiological situation, estradiol is involved in maintaining normal insulin sensitivity and to be beneficial for β-cell function. However, estradiol levels above or below the physiological range may promote insulin resistance and type II diabetes [45].

Cholecystokinin (CCK)

Cholecystokinin (CCK) is a gut peptide found in the gastrointestinal tract, predominantly in the duodenum and jejunum. This peptide has also been found in the brain where it has been associated to diverse processes such as satiety. CCK major function is the control of appetite. It stimulates the release of enzymes from the pancreas and gall bladder, coordinating digestion by increasing intestinal motility and inhibiting gastric emptying [46]. The peptide is thought to act both locally and hormonally in the gut, and as a neuromodulator in the brain.

It is well known that the administration of CCK in humans [47] as well as in animal models [48], inhibits food intake by reducing meal size and duration, an effect which is enhanced by gastric distension. Infusion of CCK at the onset of every spontaneous meal, decreases food intake by consistently limiting meal size.

CCK has a short half-life, only 1-2 minutes, its effect on food intake is rapid and brief. This peptide apparently does not regulate long-term food ingestion, if CCK is administered more than 15 minutes before a meal, it does not have any effect at reducing meal size. In rats, chronic pre-prandial administration of CCK reduces food intake, but increases at the same time meal frequency, without changes in body weight [4]. Additionally, several studies with rodents have shown that various pharmacological antagonists of CCK stimulate feeding [49].

CCK satiating action is estrogen-sensitive. The inhibitory effect of CCK on food intake is enhanced in ovariectomized rats treated with physiological doses of estradiol [50]. Experimental manipulations of CCK and estradiol have shown that estradiol cyclically increases the activity of the CCK satiation-signaling pathway resulting in the decrease of meal size and food intake during the ovulatory phase of the ovarian cycle [51-53].

Ghrelin

Ghrelin is a 28 amino acid peptide synthesized as a preprohormone. During its synthesis a modification is imposed in the hormone in the form of an n-octanoic acid bound to one of its amino acids, necessary for biological activity. Ghrelin is synthesized and released primarily from the oxyntic cells of the stomach, but also in smaller amounts from duodenum, ileum, caecum and colon [54, 55]. The hypothalamus, pituitary, placenta and kidney are also other sources of ghrelin.

Ghrelin plays an important role in the regulation of feeding behavior and energy metabolism by mainly acting at the CNS [56]. It has orexigenic effects (stimulates appetite and promotes adiposity) and increases food intake in both animals and human beings [57], via action on the hypothalamic ARC [58] by modulating hypothalamic appetite-regulating pathways, primarily the orexigenic NPY network and/or the AgRP [59].

Ghrelin concentrations increase before meals and are suppressed by the intake of nutrients [54]. An increase in circulating ghrelin levels may occur as a consequence of the anticipation of food, or may have a physiological role in initiating feeding. Administration of ghrelin, either centrally or peripherally, increases food intake and body weight and decreases fat utilization in rodents [60]. Ghrelin levels fall in response to the ingestion of food or glucose, but not following ingestion of water, suggesting that gastric distension is not a regulator [61]. Plasma ghrelin levels increase in response to food restriction, fasting and malnutritional states. Anorexic patients also have high levels of ghrelin which falls to normal after weight gain [62]. Ghrelin levels negatively correlate with body mass index in normal and obese subjects as well as in patients with anorexia nervosa [58, 62].

Although ghrelin acts as a modulator of feeding behavior and energy metabolism it has been recently implicated in reproductive physiology. It has been reported the expression

of ghrelin and its receptor in various reproductive organs, such as placenta, testis Leydig cells, ovary in rat [63, 64], and mouse embryos and endometrium [65].

Changes in the expression of ghrelin gene was demonstrated in rat ovary throughout the estrous cycle [63]. Ghrelin immunoreactivity was predominantly located in the luteal compartment of the ovary, being detected by immunostaining more intensely in steroidogenic cells from corpus luteum of the current cycle as well as in all generations of regressing corpora lutea. Its relative mRNA levels varied depending on the stage of the cycle, with the lowest levels in the highest estradiol concentration, proestrus, and peak expression values during the luteal phase of the cycle [61].

Adiponectin

Adiponectin, also called adipocyte complement-related protein (Acrp30), apM1 or adipoQ, is a 244-amino acid protein secreted from adipose tissue. Its circulating levels are up to 1,000-fold higher than other circulating hormones such as leptin and insulin [66, 67], encoded by gene APM1, which has been mapped to chromosome 3q 27 [68] and it has structural homology to complement factor C1q and collagen VIII and X [69]. Adiponectin binds to a number of receptors. Two receptors have been identified, with homology to G protein-coupled receptors and one receptor similar to the cadherin family: adiponectin receptor 1 – ADIPOR1, adiponectin receptor 2 – ADIPOR2, T-cadherin - T-Cad [70].

It has been shown that adiponectin release is significantly lower in omental than in subcutaneous adipose tissue [71]. It regulates several metabolic processes, such as glucose [72] and fatty acid metabolism [73], and energy homeostasis. It has been observed that adiponectin treatment in mice increased fatty acid oxidation in muscle [74].

In contrast to leptin, adiponectin levels are inversely correlated with body fat percentage and body mass index in adults [75, 76] while it is positively correlated with fat cell size [77, 78]. Low adiponectin concentration is related to metabolic derangements [76] such as obesity and type 2 diabetes [79], atherosclerosis [73], coronary artery disease [80], non-alcoholic fatty liver disease and an independent risk factor for metabolic syndrome [81].

Adiponectin levels in women have been found to be significantly higher than in men [75], it has been demonstrated that after neonatal castration in male and ovariectomy in female mice, tissue adiponectin content increased [82], while in other experimental studies it has been shown that androgens and estrogens also decreased adiponectin levels [82, 83]. Furthermore, there has been found decreased adiponectin levels in the last trimester of pregnancy and in patients with gestational diabetes [84]. During postmenopause, women present lower adiponectin levels, and this has been related to an increase in body mass index, which may lead to insulin resistance [85].

Glucagon

Glucagon is a 29 amino acid peptide secreted by endocrine cells of the intestinal mucosa and by the α-cells of the islets of Langerhans in the pancreas [86]. Glucagon acts in the opposite way than insulin, increasing blood glucose levels [87]. The pancreas releases glucagon when blood glucose levels fall too low, its action in the liver is to convert stored glycogen into glucose, which is released into the bloodstream. Glucagon also stimulates the release of insulin intended to be used on glucose by insulin-dependent tissues. Glucagon and insulin keep together the right blood glucose levels [87]. Studies with healthy human subjects as well as experimental animal models have shown that glucagon also has a role in the control of appetite and energy intake [88].

Gastric motility and secretion is inhibited by the presence of nutrients in the ileal lumen. Glucagon participates in the regulation of energy intake by the inhibition of gastric emptying, which limits the food intake [86, 89, 90].

Glucagon is released by the pancreas during meals, apparently largely due to cephalic phase reflexes, and each appears to act as a physiological negative feedback control of meal size in male animals. It was demonstrated that estradiol treatment in ovariectomized rats increases the satiating potency of intra-meal hepatic portal infusions of glucagon [91] and the hepatic portal infusion of glucagon antibodies (neutralization of glucagon) in the same model increased feeding in estradiol treated rats [8, 91] (Fig. (**1**)).

FOOD INTAKE DURING THE OVARY CYCLE IN DIFFERENT SPECIES

In females a number of species, feeding is closely associated with hypothalamic-pituitary-gonadal axis function. In general in the ovulatory cycle, it has been shown that in females from different species, including humans [92], rhesus monkey [93], sheep [94], rats [95, 96] and guinea pigs [93] there is a reduction of food intake around the time of ovulation, when estradiol presents its highest levels.

Menstrual cycle in women presents eating variations. Daily food intake in women is at its lowest during the peri-ovulatory period, which is usually defined as the 4 days surrounding the luteinizing hormone (LH) surge [97, 98] in which estradiol levels are maximal. Some studies also demonstrate that average daily food intake is higher during the luteal phase, than during the follicular phase [98-100]. These data show that women eat around 10% less during the peri-ovulatory window [8]. In females, estradiol and progesterone are cyclically released, however, estradiol, but not progesterone, produces the cyclic variation in food intake [8]. In women, leptin fluctuations during the menstrual cycle directly correlate with estradiol, but not with progesterone [101, 102]. The concentration of estrogens, especially estradiol, inversely correlate with feeding during many physiological states.

Rats and mice have 4-5 day ovarian cycles. In rats, around of 80 to 90% of food intake occurs nocturnally. During the night following the LH surge, the night of ovulation, there is a decrease in food intake up to 25%, accomplished by a decrease in meal size without a compensatory increase in meal frequency [10, 95, 103]. Estradiol concentration is at its highest just before the LH surge but very low during estrus. The estrous decrease in

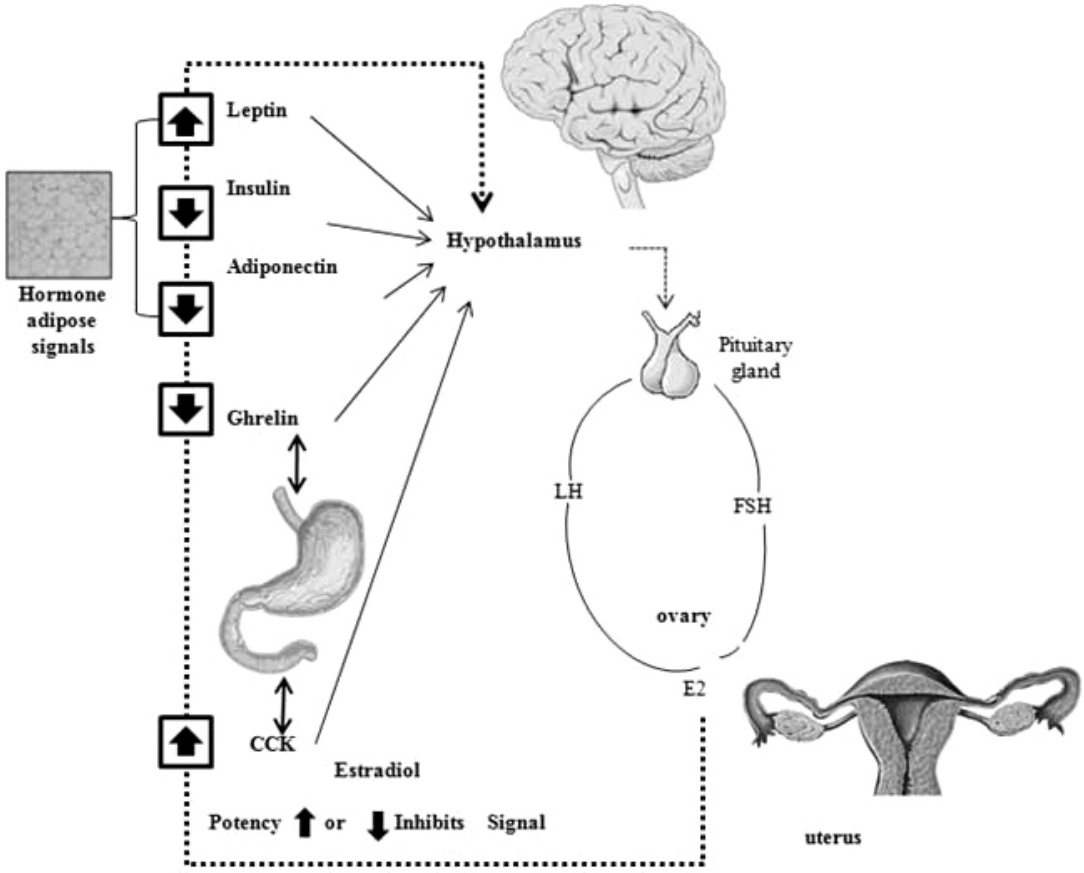

Fig. (1). Interaction between estradiol and peripheral feedback signals in the regulation of foodintake.

food intake in rats and mice is caused by preceding increase in estradiol secretion, probably because activation of ER stimulates transcription factors and the physiological effects of estradiol linger for about 12 hours. In metestrus, sex steroid secretion decreases and food intake increases. However, metestrus in rats and mice lasts only 6-8 hours and occurs diurnally, when these animals eat very little. Thus, rats and mice are poor models for eating studies during the post-ovulatory phases [8].

The cyclic change in eating apparently does not occur during anovulatory cycles [104]. It can also be suppressed in women whose eating behavior is under strong cognitive restraint [105], but it is not clear whether meal size or number is affected [8].

Ovariectomy produces an immediate increase in feeding and a 10–30% increase in body adiposity in rats and mice [53]. Estrogens reduction, as occurs in menopause and gonadectomized animals, is associated with the increase of visceral adiposity (Fig. (**2**)).

SEX DIFFERENCES IN HOMEOSTASIS OF ENERGY BALANCE

Energy balance and body fat distribution are part of the sexual dimorphism in many mammalian species including human beings. Men have less total fat and more central or intra-abdominal distribution, the adipose tissue distributed in the abdominal or visceral region (‘android’ or male-pattern body fat distribution, also called male apple profile or apple shaped) carries a much greater risk for metabolic disorders than does adipose tissue distributed subcutaneously. In contrast, women have more total fat and more gluteal/femoral subcutaneous fat distribution (‘gynoid’, or female-pattern, also called female pear profile or pear shaped) which is poorly correlated with risk for these metabolic disorders [102]. Gonadal steroids are regulators with important effects of body size, body fat content and body fat distribution [106]. Ovarian hormones protect against the metabolic syndrome. Prevalence of metabolic disorders is higher in men, than women before menopause, however, after menopause, women have an increasing possibility to suffer from metabolic disorders [107]. Intra-abdominal fat inversely varies with estrogen levels. Men have lower estrogen levels, women after menopause decline estrogen production and increase intra-abdominal adiposity, but if women receive estrogen replacement therapy there is not an increase in fat accumulation, suggesting a specific role of estrogens in limiting intra-abdominal fat mass. In contrast, androgens favor abdominal fat deposits [107] Estrogens can regulate the amount of white adipose tissue in female and males. It has been demonstrated that the absence of ERa produces adipocyte hyperplasia and hypertrophy in

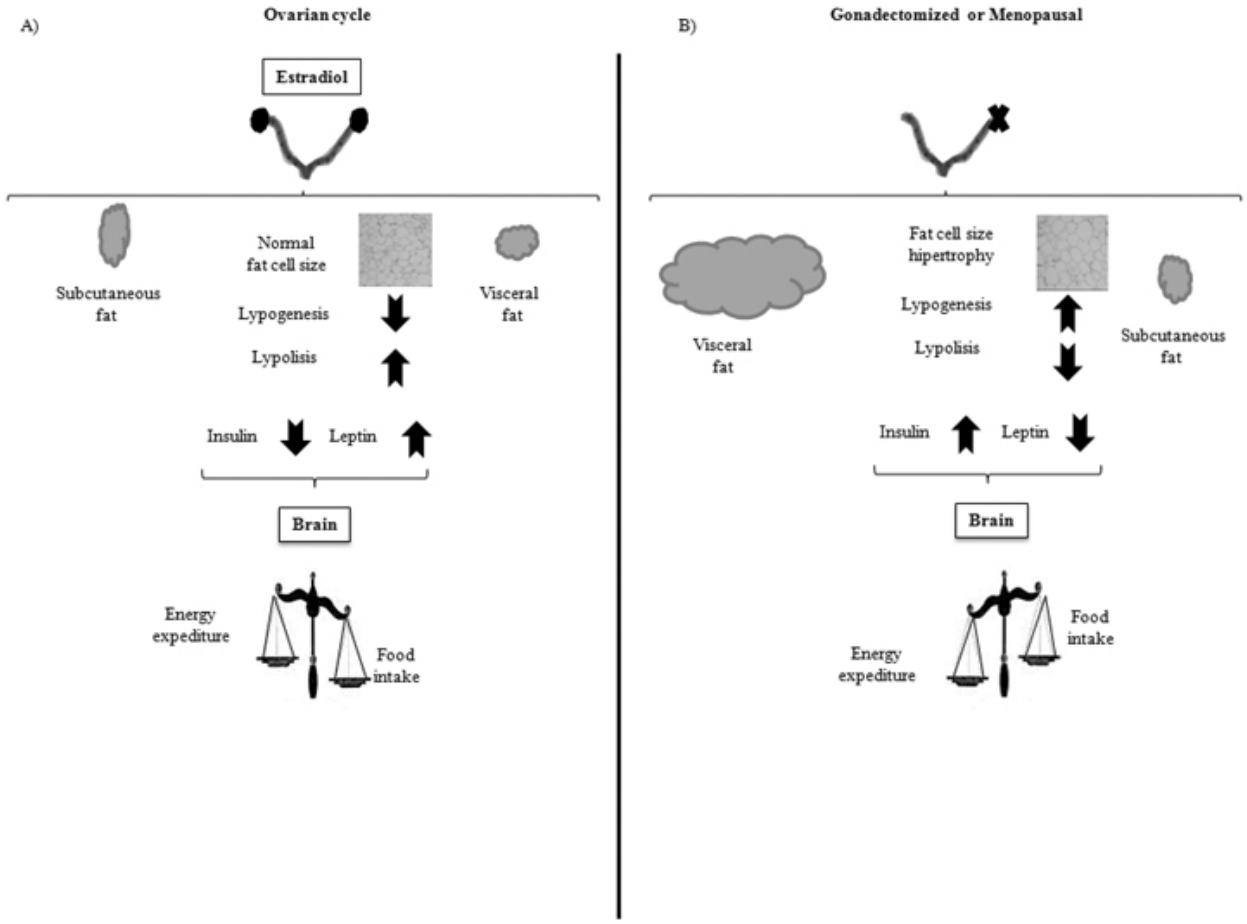

Fig. (2). Modulation of energy balance by estradiol. **A**) in the ovary cycle and **B**) in menopausal or gonadectomized conditions.

white but not in brown adipose tissue, and is accompanied by insulin resistance and glucose intolerance [19, 46]. In women, the right ratio ERa/ ERb seems to be associated with obesity as well as with serum level and production of leptin in omeotal adipose tissue [119]. In the female mice brain, the disruption or the ERa in the ventromedial nucleus of the hypothalamus leads to weight gain, increased visceral adiposity, hyperphagia, hyperglycemia and impaired energy expenditure [120]..

The amount of fat stored in adipose tissue is the balance between lipogenesis and lipolysis. When energy intake is lower than energy needs, lipolysis starts and fat stored in the form of triglycerides is broken into free fatty acids and glycerol via hormone-sensitive lipase. Visceral adipose tissue uptake of triglycerides is greater in men than in women, whereas females carry more fat subcutaneously [107].

Estradiol has long been known to inhibit feeding in animals, but the mechanisms mediating its effects have not been clear. Estrogen regulates food intake and fat distribution by acting at hypothalamus and adipose tissue level. It may probably regulate satiety signals as part of its mechanism of action. Estradiol as an indirect control of eating and meal size, produces changes in feeding behavior by modulating the central processing of both satiating and orexigenic peptides that represent direct controls of eating [10].

One of the mechanisms for estradiol to reduce body weight is increasing excitatory synapses upon POMC neural soma, resulting in both a reduction in energy intake and an increase in energy expenditure [108]. Estradiol triggers a robust increase in the number of excitatory inputs to POMC neurons in the arcuate nucleus of wild-type rats and mice. This rearrangement of synapses in the arcuate nucleus is leptin independent because it also occurred in leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice, and was paralleled by decreased food intake and body weight gain as well as increased energy expenditure [109]. Estradiol exerts direct controls on metabolism, as well, so that it plays a multifaceted role in the control of body weight. Indeed, mutant mice (of either sex) with null mutations of the ERα or of aromatase, become obese without increased feeding. Nevertheless, in ad libitum-fed, genetically normal females, the weight gain following ovariectomy and the weight loss following estradiol treatment are due mainly to altered food intake [53].

ER is expressed in the hypothalamus as well as in the adipose tissues. Catabolic action of estrogens is motivated by

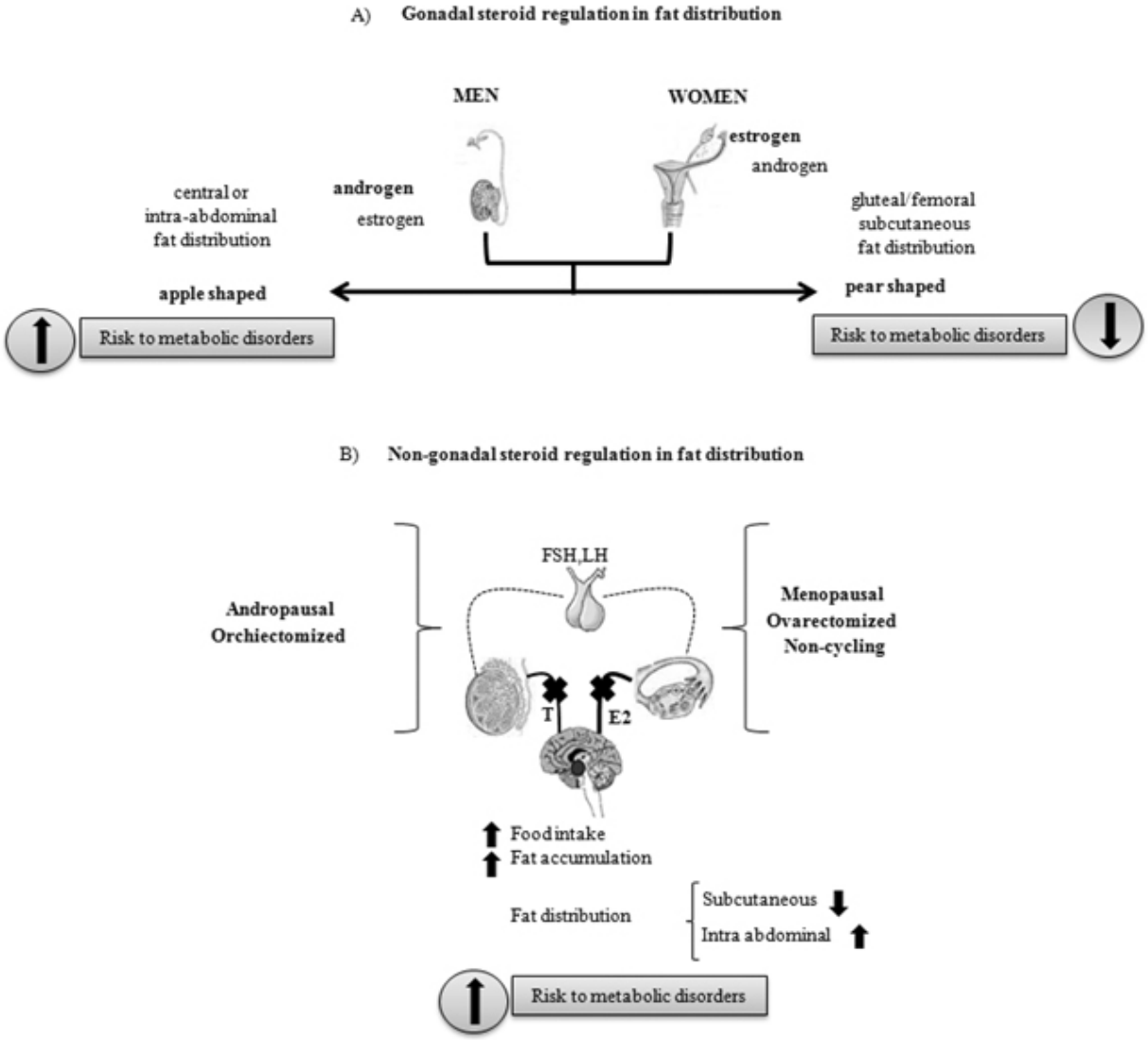

Fig. (3). A) Gonadal steroid regulation in fat distribution. **B**) Non-gonadal steroid regulation in fat distribution.

enhancing leptin sensitivity within the brain, in addition of modifying the white fat distribution to favor the subcutaneous fat deposition through activation of ER [11]. Specifically, estrogen binds on ERα in visceral adipose tissues to regulate lipid metabolism [107]. Estrogens can regulate the amount of white adipose tissue in female and males. It has been demonstrated that the absence of ERα produces adipocyte hyperplasia and hypertrophy in white but not in brown adipose tissue, and is accompanied by insulin resistance and glucose intolerance [19, 46]. In women, the right ratio ERα/ERβ seems to be associated with obesity as well as with serum level and production of leptin in omeotal adipose tissue [119]. In the female mice brain, the disruption or the ERα in the ventromedial nucleus of the hypothalamus leads to weight gain, increased visceral adiposity, hyperphagia, hyperglycemia and impaired energy expenditure [120].

The estrogen activation of membrane ER (different from ERα and ERβ) controls the electrical activity of three excitable cells relevant for energy and glucose homeostasis: insulin containing β-cells, glucagon secreting α-cells and dopamine and POMC hypothalamic neurons [37].

In males, it has been shown that androgens enhance the lipolytic capacity of cultured rat adipose precursor cells by increasing the number of β-adrenoreceptors and the activity of adenylate cyclase [102, 110]. Some studies have demonstrated the presence of androgen receptors in the adipose tissue [111]. At the adipocyte level, androgens directly modulate lipid mobilization and lipid uptake, presumably by binding to androgen receptors expressed in adipose tissue [102]. In adult male rats constant daily testosterone release results in a constant level of daily food intake, the circadian rhythm is controlled separately [8] (Fig. (**3**)).

Leptin production also presents sexual dimorphism. Serum leptin levels are higher in cycling women than in both men and postmenopausal women and remain still higher in

postmenopausal women than in men [112]. However, in rats there are controversial findings regardless the sexual dimorphism differences in leptin concentration. The higher concentrations of serum leptin in males in comparison with females have been reported by our group and others [113-115] and most likely reflects the difference in the amount of fat between males and females. In contrast, other researchers have reported that the marked sexual dimorphism in leptin plasma levels in which is much higher in females than males, is at least in part, explained by a suppressive effect of androgens on leptin production [36] and that leptin levels inversely correlated with those of testosterone [116].

Leptin expression is inhibited in human fat cell cultures exposed to testosterone or dihydrotestosterone [117]. In aging and obese men, there is increased aromatase activity and therefore a higher conversion of androgens to estrogens that has been associated to increased serum leptin [118]. Testosterone replacement normalizes elevated serum leptin levels in hypogonadal men and in castrated male rats [102]. Estradiol administration in female ovarietomized or intact male rats increases hypothalamic sensitivity to leptin and favors body fat accrual in the subcutaneous over visceral adipose depot [11, 102].

Leptin and insulin have proven different eating-inhibitory strength in male and female rats. Clegg *et al* showed that the brains of male and female rats are differentially sensitive to the catabolic actions of small doses of leptin and insulin [119]. Leptin was administered into the third cerebral ventricle of age and weight-matched male and female rats. This hormone reduced food intake in both male and female rats over 4 hours, but it only reduced food intake in females for 24 hours. The eating inhibitory efficiency after intracerebroventricular injection of leptin was not observed in ovariectomized rats, however, estradiol treatment in those animals reverted the effect [11, 119], suggesting that leptin effects are increased by estradiol [120]. The opposite happen with insulin, in which male but not female rats had a significant reduction in food intake over 24 hours after insulin administration into the third cerebral ventricle [119].

In human, plasma levels of insulin and leptin correlates with body fat content. Insulin concentration is more related with visceral fat content, in men total body fat is more closely correlated with plasma insulin levels than with plasma leptin levels; in contrast, leptin concentration is more related with subcutaneous fat content, in women total body fat is more closely associated with plasma leptin concentrations than with plasma insulin concentrations [119].

Estradiol plays an important role for the sex difference in leptin and insulin sensitivity. Leptin and estrogen receptors are localized on the same hypothalamic neurons [109], suggesting cross talk and interactions between both hormones. In addition, estradiol and its action on ERα and ERβ are implicated in control of body fat content and distribution. Mice without ERα (ERα knockout) are obese. In humans, abnormal adiposity has been associated with the Xbal polymorphism of the human ERα [121], The role of ERb is less known, although it is involved in regulating glucose transporter type 4 (GLUT4) expression in skeletal muscle and in controlling fat deposition [45].

APPETITE AND ENDOCRINE DISRUPTORS

Appetite behavior may also be affected by the endocrine disruptors. Endocrine disruptors are natural and synthetic molecules that bind to different kind of hormone receptors, either mimicking or blocking hormone action. Endocrine disruptor compounds are widely spread on the environment and display estrogenic, anti-estrogenic or anti-androgenic activity, they are lipophylic and can be stored for long periods on the adipose tissue [122]. Excessive exposure to endocrine disruptors in humans and other animals is a consequence of the modern life, having some impact in the rise of obesity at these days [123].

DEVELOPMENTAL PROGRAMMING AND FOOD INTAKE

Estrogen and its receptors may also modify the development of fetus, resulting in permanent changes to the adipocytes and cellular metabolism, and these, in turn, lead to excess visceral body fat, cardiovascular disease and type II diabetes in adulthood. Our group has shown that progesterone [124], testosterone, estradiol and corticosterone [125] serum levels are increased in pregnant protein restricted rats at the end of gestation in comparison with control pregnant rats. The overexposure of the developing fetus to steroids may predispose individual to lifelong health problems [126]. The masculinization of the female brain in early development selectively decreases the sensitivity of the adult to the eating-inhibitory effects of estradiol, but the feminization of the brain does not affect the sensitivity of the adult to the eating-stimulatory effects of testosterone [8]. The data available suggest that sex differences in adult eating partially depend on organizational effects of gonadal hormones during development. In our rat model, maternal nutrient restriction during pregnancy reduced the fat composition of brain during fetal growth generating a negatively impact in normal brain development [127] and offspring behavior [134,135]. In addition, postnatal leptin rise in pup serum was delayed by prenatal undernutrition, contributing to the development of altered appetite and metabolic disorders in later life [18]. Female offspring from rat mothers restricted during pregnancy and/or lactation, fed with control diet after weaning, presented higher testosterone serum levels during the normal estrous cycle [124] whereas in the male offspring testosterone serum concentrations were depressed [125]. Elevated cholesterol and triglycerides occurred in male pups whose mothers were nutrient restricted during pregnancy and received a normal postnatal diet, but no changes in those parameters were observed in the female offspring. However, in both, female and male pups from restricted mothers in adult life presented more visceral body fat, higher serum leptin levels, insulin resistance, as well as increased food intake in comparison to the control pups. We concluded that maternal protein restriction during either pregnancy and/or lactation alters postnatal growth, appetitive behavior, leptin physiology, triglycerides and cholesterol concentrations and modifies glucose metabolism and insulin resistance in a sex and time window of exposure-specific manner [115, 128]. Maternal

obesity also modified offspring phenotype. Our group, using high fat diet in the rat as experimental animal model, have shown that male offspring, from fat mother fed with control diet after weaning presented an increase in fat cell size and mass, serum triglycerides, leptin and insulin concentrations [129], leading to developmental programming of offspring who are predisposed to obesity, diabetes, hypertension, appetite disorders and other chronic disease.

SUMMARY AND CONCLUSIONS

In the last years the knowledge of the physiological systems and networks that regulate food intake and body weight has increased immensely. Overweight and obesity is the result of an imbalance between energy intake and expenditure with important gender differences in the prevalence of these metabolic diseases. These sex dissimilarities could be related to the different sex hormone profile in men and women. The study of gender differences in appetite has contributed as an important part of the physiology of eating. The link between steroid hormones and energy balance is relevant to develop effective treatment for obese patients. A better understanding of the gender differences in the regulation of food intake and fat accumulation will help to develop drugs that reverse the obesity epidemic. Many treatments are effective in the short term, but long term efficacy is priority, therefore, the most effective and safe treatment remains in the modification of the quality and quantity of food intake and to increase energy expenditure with exercise and changes in life style.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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ABBREVIATIONS

AgRP = Agouti-related protein

CART = amphetamine-regulated transcript

AR = androgen receptor

CNS = central nervous system

CCK = cholecystokinin

DHT = 5α-dihydrotestosterone

α and β = estrogen receptors ERα and ERβ

GLP-1 = glucagon-like peptide-1

GSH = gonadal steroid hormones

GSH-R = growth hormone secretagoue receptor

Ob-R = leptin receptor

MSH = melanocortin

Y NPY = neuropeptide

OXM = Oxyntomodulin

PP = pancreatic polypeptide

PR = progesterone receptor

POMC = pro-opiomelanocortin

IRS = receptor substrates

REFERENCES

[1] Druce, M.; Bloom, S. R. The regulation of appetite. *Arch. Dis. Child*, **2006**, *91*, 183-7.

[2] Small, C. J.; Parkinson, J. R.; Bloom, S. R. Novel therapeutic targets for appetite regulation. *Curr. Opin. Investig. Drugs*, **2005**, *6*, 369-72.

[3] Suzuki, K.; Simpson, K. A.; Minnion, J. S.; Shillito, J. C.; Bloom, S. R. The role of gut hormones and the hypothalamus in appetite regulation. *Endocr. J.*, **2010**, *57*, 359-72.

[4] Wynne, K.; Stanley, S.; McGowan, B.; Bloom, S. Appetite control. *J. Endocrinol.*, **2005**, 184, 291-318.

[5] Chaudhri, O.; Small, C.; Bloom, S. Gastrointestinal hormones regulating appetite. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, **2006**, *361*, 1187-209.

[6] Gruber, C. J.; Tschugguel, W.; Schneeberger, C.; Huber, J. C. Production and actions of estrogens. *N. Engl. J. Med.*, **2002**, *346*, 340-52.

[7] Vanderschueren, D.; Vandenput, L.; Boonen, S.; Lindberg, M. K.; Bouillon, R.; Ohlsson, C. Androgens and bone. *Endocr. Rev.*, **2004**, *25*, 389-425.

[8] Asarian, L.; Geary, N. Modulation of appetite by gonadal steroid hormones. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, **2006**, *361*, 1251-63.

[9] Ozawa, H. Steroid Hormones, their receptors and neuroendocrine system. *J. Nippon. Med. Sch.*, **2005**, *72*, 316-25.

[10] Butera, P. C. Estradiol and the control of food intake. *Physiol. Behav.* **2010**, *99*, 175-80.

[11] Clegg, D. J.; Brown, L. M.; Woods, S. C.; Benoit, S. C. Gonadal hormones determine sensitivity to central leptin and insulin. *Diabetes*, **2006**, *55*, 978-87.

[12] Campfield, L. A.; Smith, F. J.; Guisez, Y.; Devos, R.; Burn, P. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science*, **1995**, *269*, 546-9.

[13] Pelleymounter, M. A.; Cullen, M. J.; Baker, M. B.; Hecht, R.; Winters, D.; Boone, T.; Collins, F. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science*, **1995**, 269, 540-3.

[14] Tartaglia, L. A.; Dembski, M.; Weng, X.; Deng, N.; Culpepper, J.; Devos, R.; Richards, G. J.; Campfield, L. A.; Clark, F. T.; Deeds, J.; Muir, C.; Sanker, S.; Moriarty, A.; Moore, K. J.; Smutko, J. S.; Mays, G. G.; Wool, E. A.; Monroe, C. A.; Tepper, R. I. Identification and expression cloning of a leptin receptor, OB-R. *Cell*, **1995**, *83*, 1263-71.

[15] Tartaglia, L. A. The leptin receptor. *J. Biol. Chem.* **1997**, *272*, 6093-6.

[16] Ahima, R. S.; Prabakaran, D.; Flier, J. S. Postnatal leptin surge and regulation of circadian rhythm of leptin by feeding. Implications for energy homeostasis and neuroendocrine function. *J. Clin. Invest.*, **1998**, *101*, 1020-7.

[17] Rayner, D. V.; Dalgliesh, G. D.; Duncan, J. S.; Hardie, L. J.; Hoggard, N.; Trayhurn, P. Postnatal development of the ob gene system: elevated leptin levels in suckling fa/fa rats. *Am. J. Physiol.*, **1997**, *273*, R446-50.

[18] Bautista, C. J.; Boeck, L.; Larrea, F.; Nathanielsz, P. W.; Zambrano, E. Effects of a maternal low protein isocaloric diet on milk leptin and progeny serum leptin concentration and appetitive behavior in the first 21 days of neonatal life in the rat. *Pediatr. Res.*, **2008**, *63*, 358-63.

[19] Heine, P. A.; Taylor, J. A.; Iwamoto, G. A.; Lubahn, D. B.; Cooke, P. S. Increased adipose tissue in male and female estrogen receptor alpha knockout mice. *Proc. Natl. Acad. Sci. U.S.A.*, **2000**, *97*, 12729- 34.

[20] Vickers, M. H.; Gluckman, P. D.; Coveny, A. H.; Hofman, P. L.; Cutfield, W. S.; Gertler, A.; Breier, B. H.; Harris, M. Neonatal leptin treatment reverses developmental programming. *Endocrinology*, **2005**, *146*, 4211-6.

[21] Ostlund, R. E., Jr.; Yang, J. W.; Klein, S.; Gingerich, R. Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. *J. Clin .Endocrinol. Metab.*, **1996**, *81*, 3909-13.

[22] Devaskar, S. U.; Ollesch, C.; Rajakumar, R. A.; Rajakumar, P. A. Developmental changes in ob gene expression and circulating leptin peptide concentrations. *Biochem. Biophys. Res. Commun.*, **1997**, *238*, 44-7.

[23] Mistry, A. M.; Swick, A.; Romsos, D. R. Leptin alters metabolic rates before acquisition of its anorectic effect in developing neonatal mice. *Am. J. Physiol.*, **1999**, *277*, R742-7.

[24] Alonso, A.; Fernandez, R.; Moreno, M.; Ordonez, P.; Diaz, F.; Gonzalez, C. Leptin and its receptor are controlled by 17beta-estradiol in peripheral tissues of ovariectomized rats. *Exp. Biol. Med. (Maywood)*, **2007**, *232*, 542-9.

[25] Brann, D. W.; De Sevilla, L.; Zamorano, P. L.; Mahesh, V. B. Regulation of leptin gene expression and secretion by steroid hormones. *Steroids*, **1999**, *64*, 659-63.

[26] Machinal, F.; Dieudonne, M. N.; Leneveu, M. C.; Pecquery, R.; Giudicelli, Y. *In vivo* and *in vitro* ob gene expression and leptin secretion in rat adipocytes: evidence for a regional specific regulation by sex steroid hormones. *Endocrinology*, **1999**, *140*, 1567-74.

[27] Schwartz, M. W.; Figlewicz, D. P.; Baskin, D. G.; Woods, S. C.; Porte, D., Jr. Insulin in the brain: a hormonal regulator of energy balance. *Endocr. Rev.*, **1992**, *13*, 387-414.

[28] Baura, G. D.; Foster, D. M.; Porte, D., Jr.; Kahn, S. E.; Bergman, R. N.; Cobelli, C.; Schwartz, M. W. Saturable transport of insulin from plasma into the central nervous system of dogs *in vivo*. A mechanism for regulated insulin delivery to the brain. *J. Clin. Invest.*, **1993**, *92*, 1824-30.

[29] Polonsky, K. S.; Given, B. D.; Van Cauter, E. Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *J. Clin. Invest.*, **1988**, *81*, 442-8.

[30] Porte, D., Jr.; Baskin, D. G.; Schwartz, M. W. Leptin and insulin action in the central nervous system. *Nutr. Rev.*, **2002**, *60*, S20-9; discussion S68-84, 85-7.

[31] Taniguchi, C. M.; Emanuelli, B.; Kahn, C. R. Critical nodes in signalling pathways: insights into insulin action. *Nat. Rev. Mol. Cell. Biol.*, **2006**, *7*, 85-96.

[32] White, M. F. The IRS-signalling system: a network of docking proteins that mediate insulin action. *Mol. Cell. Biochem.*, **1998**, *182*, 3-11.

[33] Baskin, D. G.; Schwartz, M. W.; Sipols, A. J.; D'Alessio, D. A.; Goldstein, B. J.; White, M. F. Insulin receptor substrate-1 (IRS-1) expression in rat brain. *Endocrinology*, **1994**, *134*, 1952-5.

[34] Bruning, J. C.; Gautam, D.; Burks, D. J.; Gillette, J.; Schubert, M.; Orban, P. C.; Klein, R.; Krone, W.; Muller-Wieland, D.; Kahn, C. R. Role of brain insulin receptor in control of body weight and reproduction. *Science*, **2000**, *289*, 2122-5.

[35] Corp, E. S.; Woods, S. C.; Porte, D., Jr.; Dorsa, D. M.; Figlewicz, D. P.; Baskin, D. G. Localization of 125I-insulin binding sites in the rat hypothalamus by quantitative autoradiography. *Neurosci. Lett.*, **1986**, *70*, 17-22.

[36] Marks, J. L.; Porte, D., Jr.; Stahl, W. L.; Baskin, D. G. Localization of insulin receptor mRNA in rat brain by in situ hybridization. *Endocrinology*, **1990**, *127*, 3234-6.

[37] Coll, A. P.; Farooqi, I. S.; O'Rahilly, S. The hormonal control of food intake. *Cell*, **2007**, *129*, 251-62.

[38] Ropero, A. B.; Alonso-Magdalena, P.; Quesada, I.; Nadal, A. The role of estrogen receptors in the control of energy and glucose homeostasis. *Steroids*, **2008**, *73*, 874-9.

[39] Heine, P. A.; Taylor, J. A.; Iwamoto, G. A.; Lubahn, D. B.; Cooke, P. S. Increased adipose tissue in male and female estrogen receptor-alpha knockout mice. *Proc. Natl. Acad. Sci. U.S.A.*, **2000**, *97*, 12729-34.

[40] Takeda, K.; Toda, K.; Saibara, T.; Nakagawa, M.; Saika, K.; Onishi, T.; Sugiura, T.; Shizuta, Y. Progressive development of insulin resistance phenotype in male mice with complete aromatase (CYP19) deficiency. *J. Endocrinol.*, **2003**, *176*, 237-46.

[41] Alonso-Magdalena, P.; Ropero, A. B.; Carrera, M. P.; Cederroth, C. R.; Baquie, M.; Gauthier, B. R.; Nef, S.; Stefani, E.; Nadal, A. Pancreatic insulin content regulation by the estrogen receptor ER alpha. *PLoS. One.*, **2008**, *3*, e2069.

[42] Livingstone, C.; Collison, M. Sex steroids and insulin resistance. *Clin. Sci. (Lond)*, **2002**, *102*, 151-66.

[43] Godsland, I. F. The influence of female sex steroids on glucose metabolism and insulin action. *J. Intern. Med. Suppl.*, **1996**, *738*, 1-60.

[44] Godsland, I. F. Oestrogens and insulin secretion. *Diabetologia*, **2005**, *48*, 2213-20.

[45] Nadal, A.; Alonso-Magdalena, P.; Soriano, S.; Quesada, I.; Ropero, A. B. The pancreatic beta-cell as a target of estrogens and xenoestrogens: Implications for blood glucose homeostasis and diabetes. *Mol. Cell. Endocrinol.*, **2009**, *304*, 63-8.

[46] Gonzalez, C.; Alonso, A.; Diaz, F.; Patterson, A. M. Dose- and time-dependent effects of 17beta-oestradiol on insulin sensitivity in insulin-dependent tissues of rat: implications of IRS-1. *J. Endocrinol.*, **2003**, *176*, 367-79.

[47] Takeda, K.; Toda, K.; Saibara, T.; Nakagawa, M.; Saika, K.; Onishi, T.; Sugiura, T.; Shizuta, Y. Progressive development of insulin resistance phenotype in male mice with complete aromatase (CYP19) deficiency. *J. Endocrinol.*, **2003**, *176*, 237-46.

[48] Liddle, R. A.; Goldfine, I. D.; Rosen, M. S.; Taplitz, R. A.; Williams, J. A. Cholecystokinin bioactivity in human plasma. Molecular forms, responses to feeding, and relationship to gallbladder contraction. *J. Clin. Invest.*, **1985**, *75*, 1144-52.

[49] Kissileff, H. R.; Pi-Sunyer, F. X.; Thornton, J.; Smith, G. P. C-terminal octapeptide of cholecystokinin decreases food intake in man. *Am. J. Clin. Nutr.*, **1981**, *34*, 154-60.

[50] Gibbs, J.; Young, R. C.; Smith, G. P. Cholecystokinin decreases food intake in rats. *J. Comp. Physiol. Psychol.*, **1973**, *84*, 488-95.

[51] Dulawa, S. C.; Vanderweele, D. A. Cholecystokinin and estradiol synergistically potentiate satiety in rats. *Peptides*, **1994**, *15*, 913-8.

[52] Butera, P. C.; Bradway, D. M.; Cataldo, N. J. Modulation of the satiety effect of cholecystokinin by estradiol. *Physiol. Behav.*, **1993**, *53*, 1235-8.

[53] Wager-Srdar, S. A.; Gannon, M.; Levine, A. S. The effect of cholecystokinin on food intake in gonadectomized and intact rats: the influence of sex hormones. *Physiol. Behav.*, **1987**, *40*, 25-8.

[54] Asarian, L.; Geary, N. Cyclic estradiol treatment phasically potentiates endogenous cholecystokinin's satiating action in ovariectomized rats. *Peptides*, **1999**, *20*, 445-50.

[55] Geary, N. Estradiol, CCK and satiation. *Peptides*, **2001**, *22*, 1251-63.

[56] Date, Y.; Kojima, M.; Hosoda, H.; Sawaguchi, A.; Mondal, M. S.; Suganuma, T.; Matsukura, S.; Kangawa, K.; Nakazato, M. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology*, **2000**, *141*, 4255-61.

[57] Sakata, I.; Nakamura, K.; Yamazaki, M.; Matsubara, M.; Hayashi, Y.; Kangawa, K.; Sakai, T. Ghrelin-producing cells exist as two types of cells, closed- and opened-type cells, in the rat gastrointestinal tract. *Peptides*, **2002**, *23*, 531-6.

[58] Gale, S. M.; Castracane, V. D.; Mantzoros, C. S. Energy homeostasis, obesity and eating disorders: recent advances in endocrinology. *J. Nutr.*, **2004**, *134*, 295-8.

[59] Muller, E. E.; Locatelli, V.; Cocchi, D. Neuroendocrine control of growth hormone secretion. *Physiol. Rev.*, **1999**, *79*, 511-607.

[60] Cummings, D. E.; Weigle, D. S.; Frayo, R. S.; Breen, P. A.; Ma, M. K.; Dellinger, E. P.; Purnell, J. Q. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N. Engl. J. Med.*, **2002**, *346*, 1623-30.

[61] Chen, H. Y.; Trumbauer, M. E.; Chen, A. S.; Weingarth, D. T.; Adams, J. R.; Frazier, E. G.; Shen, Z.; Marsh, D. J.; Feighner, S. D.; Guan, X. M.; Ye, Z.; Nargund, R. P.; Smith, R. G.; Van der Ploeg, L. H.; Howard, A. D.; MacNeil, D. J.; Qian, S. Orexigenic action of peripheral ghrelin is mediated by neuropeptide Y and agouti-related protein. *Endocrinology*, **2004**, *145*, 2607-12.

[62] Tschop, M.; Smiley, D. L.; Heiman, M. L. Ghrelin induces adiposity in rodents. *Nature*, **2000**, *407*, 908-13.

[63] Budak, E.; Fernandez Sanchez, M.; Bellver, J.; Cervero, A.; Simon, C.; Pellicer, A. Interactions of the hormones leptin, ghrelin, adiponectin, resistin, and PYY3-36 with the reproductive system. *Fertil. Steril.*, **2006**, *85*, 1563-81.

[64] Otto, B.; Cuntz, U.; Fruehauf, E.; Wawarta, R.; Folwaczny, C.; Riepl, R. L.; Heiman, M. L.; Lehnert, P.; Fichter, M.; Tschop, M. Weight gain decreases elevated plasma ghrelin concentrations of patients with anorexia nervosa. *Eur. J. Endocrinol.*, **2001**, *145*, 669-73.

[65] Caminos, J. E.; Tena-Sempere, M.; Gaytan, F.; Sanchez-Criado, J. E.; Barreiro, M. L.; Nogueiras, R.; Casanueva, F. F.; Aguilar, E.; Dieguez, C. Expression of ghrelin in the cyclic and pregnant rat ovary. *Endocrinology*, **2003**, *144*, 1594-602.

[66] Tena-Sempere, M.; Barreiro, M. L.; Gonzalez, L. C.; Gaytan, F.; Zhang, F. P.; Caminos, J. E.; Pinilla, L.; Casanueva, F. F.; Dieguez, C.; Aguilar, E. Novel expression and functional role of ghrelin in rat testis. *Endocrinology*, **2002**, *143*, 717-25.

[67] Kawamura, K.; Sato, N.; Fukuda, J.; Kodama, H.; Kumagai, J.; Tanikawa, H.; Nakamura, A.; Honda, Y.; Sato, T.; Tanaka, T. Ghrelin inhibits the development of mouse preimplantation embryos *in vitro*. *Endocrinology*, **2003**, 144, 2623-33.

[68] Maeda, N.; Shimomura, I.; Kishida, K.; Nishizawa, H.; Matsuda, M.; Nagaretani, H.; Furuyama, N.; Kondo, H.; Takahashi, M.; Arita, Y.; Komuro, R.; Ouchi, N.; Kihara, S.; Tochino, Y.; Okutomi, K.; Horie, M.; Takeda, S.; Aoyama, T.; Funahashi, T.; Matsuzawa, Y. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat. Med.*, **2002**, *8*, 731-7.

[69] Nakano, Y.; Tobe, T.; Choi-Miura, N. H.; Mazda, T.; Tomita, M. Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. *J. Biochem.*, **1996**, *120*, 803-12.

[70] Vasseur, F.; Lepretre, F.; Lacquemant, C.; Froguel, P. The genetics of adiponectin. *Curr. Diab. Rep.*, **2003**, *3*, 151-8.

[71] Nedvidkova, J.; Smitka, K.; Kopsky, V.; Hainer, V. Adiponectin, an adipocyte-derived protein. *Physiol. Res.*, **2005**, *54*, 133-40.

[72] Yamauchi, T.; Kamon, J.; Ito, Y.; Tsuchida, A.; Yokomizo, T.; Kita, S.; Sugiyama, T.; Miyagishi, M.; Hara, K.; Tsunoda, M.; Murakami, K.; Ohteki, T.; Uchida, S.; Takekawa, S.; Waki, H.; Tsuno, N. H.; Shibata, Y.; Terauchi, Y.; Froguel, P.; Tobe, K.; Koyasu, S.; Taira, K.; Kitamura, T.; Shimizu, T.; Nagai, R.; Kadowaki, T. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature*, **2003**, *423*, 762-9.

[73] Berk, E. S.; Kovera, A. J.; Boozer, C. N.; Pi-Sunyer, F. X.; Johnson, J. A.; Albu, J. B. Adiponectin levels during low- and high-fat eucaloric diets in lean and obese women. *Obes. Res.*, **2005**, *13*, 1566-71.

[74] Berg, A. H.; Combs, T. P.; Du, X.; Brownlee, M.; Scherer, P. E. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat. Med.*, **2001**, *7*, 947-53.

[75] Diez, J. J.; Iglesias, P. The role of the novel adipocyte-derived hormone adiponectin in human disease. *Eur. J. Endocrinol.*, **2003**, *148*, 293-300.

[76] Fruebis, J.; Tsao, T. S.; Javorschi, S.; Ebbets-Reed, D.; Erickson, M. R.; Yen, F. T.; Bihain, B. E.; Lodish, H. F. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc. Natl. Acad. Sci. U.S.A.*, **2001**, *98*, 2005-10.

[77] Arita, Y.; Kihara, S.; Ouchi, N.; Takahashi, M.; Maeda, K.; Miyagawa, J.; Hotta, K.; Shimomura, I.; Nakamura, T.; Miyaoka, K.; Kuriyama, H.; Nishida, M.; Yamashita, S.; Okubo, K.; Matsubara, K.; Muraguchi, M.; Ohmoto, Y.; Funahashi, T.; Matsuzawa, Y. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem. Biophys. Res. Commun.*, **1999**, *257*, 79-83.

[78] Haluzik, M.; Parizkova, J.; Haluzik, M. M. Adiponectin and its role in the obesity-induced insulin resistance and related complications. *Physiol. Res.*, **2004**, *53*, 123-9.

[79] Ukkola, O.; Santaniemi, M. Adiponectin: a link between excess adiposity and associated comorbidities? *J. Mol. Med.*, **2002**, *80*, 696-702.

[80] Scherer, P. E.; Williams, S.; Fogliano, M.; Baldini, G.; Lodish, H. F. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J. Biol. Chem.*, **1995**, *270*, 26746-9.

[81] Hotta, K.; Funahashi, T.; Arita, Y.; Takahashi, M.; Matsuda, M.; Okamoto, Y.; Iwahashi, H.; Kuriyama, H.; Ouchi, N.; Maeda, K.; Nishida, M.; Kihara, S.; Sakai, N.; Nakajima, T.; Hasegawa, K.; Muraguchi, M.; Ohmoto, Y.; Nakamura, T.; Yamashita, S.; Hanafusa, T.; Matsuzawa, Y. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc. Biol.*, **2000**, *20*, 1595-9.

[82] Ouchi, N.; Kihara, S.; Arita, Y.; Maeda, K.; Kuriyama, H.; Okamoto, Y.; Hotta, K.; Nishida, M.; Takahashi, M.; Nakamura, T.; Yamashita, S.; Funahashi, T.; Matsuzawa, Y. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation*, **1999**, *100*, 2473-6.

[83] Renaldi, O.; Pramono, B.; Sinorita, H.; Purnomo, L. B.; Asdie, R. H.; Asdie, A. H. Hypoadiponectinemia: a risk factor for metabolic syndrome. *Acta Med. Indones.*, **2009**, *41*, 20-4.

[84] Combs, T. P.; Berg, A. H.; Rajala, M. W.; Klebanov, S.; Iyengar, P.; Jimenez-Chillaron, J. C.; Patti, M. E.; Klein, S. L.; Weinstein, R. S.; Scherer, P. E. Sexual differentiation, pregnancy, calorie restriction, and aging affect the adipocyte-specific secretory protein adiponectin. *Diabetes*, **2003**, *52*, 268-76.

[85] Nishizawa, H.; Shimomura, I.; Kishida, K.; Maeda, N.; Kuriyama, H.; Nagaretani, H.; Matsuda, M.; Kondo, H.; Furuyama, N.; Kihara, S.; Nakamura, T.; Tochino, Y.; Funahashi, T.; Matsuzawa, Y. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. *Diabetes*, **2002**, *51*, 2734-41.

[86] Mazaki-Tovi, S.; Kanety, H.; Sivan, E. Adiponectin and human pregnancy. *Curr. Diab. Rep.*, **2005**, *5*, 278-81.

[87] Tapan, S.; Dogru, T.; Sonmez, A.; Kurt, I.; Erbil, M. K. Circulating adiponectin levels in post-menopausal women with and without osteoporosis. *Clin. Biochem.* 43, 705; author reply 706.

[88] Flint, A.; Raben, A.; Astrup, A.; Holst, J. J. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J. Clin. Invest.*, **1998**, *101*, 515-20.

[89] Kieffer, T. J.; Habener, J. F. The glucagon-like peptides. *Endocr. Rev.* **1999**, *20*, 876-913.

[90] Gutzwiller, J. P.; Drewe, J.; Goke, B.; Schmidt, H.; Rohrer, B.; Lareida, J.; Beglinger, C. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. *Am. J. Physiol.*, **1999**, *276*, R1541-4.

[91] Holst, J. J. Enteroglucagon. *Annu. Rev. Physiol.*, **1997**, *59*, 257-71.

[92] Wettergren, A.; Schjoldager, B.; Mortensen, P. E.; Myhre, J.; Christiansen, J.; Holst, J. J. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. *Dig. Dis. Sci.*, **1993**, *38*, 665-73.

[93] Geary, N.; Asarian, L. Estradiol increases glucagon's satiating potency in ovariectomized rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **2001**, *281*, R1290-4.

[94] Dalvit-McPhillips, S. P. The effect of the human menstrual cycle on nutrient intake. *Physiol. Behav.*, **1983**, *31*, 209-12.

[95] Czaja, J. A.; Goy, R. W. Ovarian hormones and food intake in female guinea pigs and rhesus monkeys. *Horm. Behav.*, **1975**, *6*, 329-49.

[96] Tarttelin, M. F. Cyclical variations in food and water intakes in ewes. *J. Physiol.*, **1968**, *195*, 29P-31P.

[97] Blaustein, J. D.; Wade, G. N. Ovarian influences on the meal patterns of female rats. *Physiol. Behav.*, **1976**, *17*, 201-8.

[98] ter Haar, M. B. Circadian and estrual rhythms in food intake in the rat. *Horm. Behav.*, **1972**, *3*, 213-9.

[99] Gong, E. J.; Garrel, D.; Calloway, D. H. Menstrual cycle and voluntary food intake. *Am. J. Clin. Nutr.*, **1989**, *49*, 252-8.

[100] Lyons, P. M.; Truswell, A. S.; Mira, M.; Vizzard, J.; Abraham, S. F. Reduction of food intake in the ovulatory phase of the menstrual cycle. *Am. J. Clin. Nutr.*, **1989**, *49*, 1164-8.

[101] Lissner, L.; Stevens, J.; Levitsky, D. A.; Rasmussen, K. M.; Strupp, B. J. Variation in energy intake during the menstrual cycle: implications for food-intake research. *Am. J. Clin. Nutr.*, **1988**, *48*, 956-62.

[102] Pelkman, C. L.; Chow, M.; Heinbach, R. A.; Rolls, B. J. Short-term effects of a progestational contraceptive drug on food intake, resting energy expenditure, and body weight in young women. *Am. J. Clin. Nutr.*, **2001**, *73*, 19-26.

[103] Quinton, N. D.; Smith, R. F.; Clayton, P. E.; Gill, M. S.; Shalet, S.; Justice, S. K.; Simon, S. A.; Walters, S.; Postel-Vinay, M. C.; Blakemore, A. I.; Ross, R. J. Leptin binding activity changes with age: the link between leptin and puberty. *J. Clin. Endocrinol. Metab.*, **1999**, *84*, 2336-41.

[104] Shi, H.; Clegg, D. J. Sex differences in the regulation of body weight. *Physiol. Behav.*, **2009**, *97*, 199-204.

[105] Geary, N.; Asarian, L. Cyclic estradiol treatment normalizes body weight and test meal size in ovariectomized rats. *Physiol. Behav.*, **1999**, *67*, 141-7.

[106] Rock, C. L.; Gorenflo, D. W.; Drewnowski, A.; Demitrack, M. A. Nutritional characteristics, eating pathology, and hormonal status in young women. *Am. J. Clin. Nutr.*, **1996**, *64*, 566-71.

[107] Dye, L.; Blundell, J. E. Menstrual cycle and appetite control: implications for weight regulation. *Hum. Reprod.* **1997**, *12*, 1142-51.

[108] Nilsson, C.; Niklasson, M.; Eriksson, E.; Bjorntorp, P.; Holmang, A. Imprinting of female offspring with testosterone results in insulin resistance and changes in body fat distribution at adult age in rats. *J. Clin. Invest.*, **1998**, *101*, 74-8.

[109] Shi, H.; Seeley, R. J.; Clegg, D. J. Sexual differences in the control of energy homeostasis. *Front Neuroendocrinol*, **2009**, *30*, 396-404.

[110] Gao, Q.; Mezei, G.; Nie, Y.; Rao, Y.; Choi, C. S.; Bechmann, I.; Leranth, C.; Toran-Allerand, D.; Priest, C. A.; Roberts, J. L.; Gao, X. B.; Mobbs, C.; Shulman, G. I.; Diano, S.; Horvath, T. L. Anorectic estrogen mimics leptin's effect on the rewiring of melanocortin cells and Stat3 signaling in obese animals. *Nat. Med.* **2007**, *13*, 89-94.

[111] Diano, S.; Kalra, S. P.; Sakamoto, H.; Horvath, T. L. Leptin receptors in estrogen receptor-containing neurons of the female rat hypothalamus. *Brain. Res.*, **1998**, *812*, 256-9.

[112] Sjogren, J.; Li, M.; Bjorntorp, P. Androgen hormone binding to adipose tissue in rats. *Biochim. Biophys. Acta.*, **1995**, *1244*, 117-20.

[113] Dieudonne, M. N.; Pecquery, R.; Boumediene, A.; Leneveu, M. C.; Giudicelli, Y. Androgen receptors in human preadipocytes and adipocytes: regional specificities and regulation by sex steroids. *Am. J. Physiol.*, **1998**, *274*, C1645-52.

[114] Rosenbaum, M.; Nicolson, M.; Hirsch, J.; Heymsfield, S. B.; Gallagher, D.; Chu, F.; Leibel, R. L. Effects of gender, body composition, and menopause on plasma concentrations of leptin. *J. Clin. Endocrinol. Metab.*, **1996**, *81*, 3424-7.

[115] Franko, K. L.; Forhead, A. J.; Fowden, A. L. Differential effects of prenatal stress and glucocorticoid administration on postnatal growth and glucose metabolism in rats. *J. Endocrinol.*, **2010**, *204*, 319-29.

[116] Pinos, H.; Ortega, E.; Carrillo, B.; Perez-Izquierdo, M. A.; Collado, P. Differential effects of undernourishment and nutritional rehabilitation on serum leptin levels in male and female rats. *Neurochem. Res.*, **2007**, *32*, 407-13.

[117] Zambrano, E.; Bautista, C. J.; Deas, M.; Martinez-Samayoa, P. M.; Gonzalez-Zamorano, M.; Ledesma, H.; Morales, J.; Larrea, F.; Nathanielsz, P. W. A low maternal protein diet during pregnancy and lactation has sex- and window of exposure-specific effects on offspring growth and food intake, glucose metabolism and serum leptin in the rat. *J. Physiol.*, **2006**, *571*, 221-30.

[118] Kristensen, K.; Pedersen, S. B.; Richelsen, B. Regulation of leptin by steroid hormones in rat adipose tissue. *Biochem. Biophys. Res. Commun.*, **1999**, *259*, 624-30.

[119] Wabitsch, M.; Blum, W. F.; Muche, R.; Braun, M.; Hube, F.; Rascher, W.; Heinze, E.; Teller, W.; Hauner, H. Contribution of androgens to the gender difference in leptin production in obese children and adolescents. *J. Clin. Invest.*, **1997**, *100*, 808-13.

[120] Morley, J. E.; Perry, H. M., 3rd. Androgen deficiency in aging men: role of testosterone replacement therapy. *J. Lab. Clin. Med.*, **2000**, *135*, 370-8.

[121] Shin, J.H.; Hur, J.Y.; Seo, H.S.; Jeong, Y.A.; Lee, J.K.; Oh, M.J.; Kim, T.; Saw, H.S.; Kim, S.H. The ratio of estrogen receptor alpha to estrogen receptor beta in adipose tissue is associated with leptin production and obesity. *Steroids*, **2007**, *72*, 592-9.

[122] Musatov, S.; Chen, W.; Pfaff, D.W.; Mobbs, C.V.; Yang, X.J.; Clegg, D.J.; Kaplitt, M.G.; Ogawa, S. Silencing of estrogen receptor alpha in the ventromedial nucleus of hypothalamus leads to metabolic syndrome. *Proc. Natl. Acad. Sci. U.S.A.*, **2007**, *104*, 2501-6.

[123] Clegg, D. J.; Riedy, C. A.; Smith, K. A.; Benoit, S. C.; Woods, S. C. Differential sensitivity to central leptin and insulin in male and female rats. *Diabetes*, **2003**, 52, 682-7.

[124] Ainslie, D. A.; Morris, M. J.; Wittert, G.; Turnbull, H.; Proietto, J.; Thorburn, A. W. Estrogen deficiency causes central leptin insensitivity and increased hypothalamic neuropeptide Y. *Int. J. Obes. Relat. Metab. Disord.*, **2001**, *25*, 1680-8.

[125] Okura, T.; Koda, M.; Ando, F.; Niino, N.; Ohta, S.; Shimokata, H. Association of polymorphisms in the estrogen receptor alpha gene with body fat distribution. *Int. J. Obes. Relat. Metab. Disord.* **2003**, *27*, 1020-7.

[126] Guzman, C.; Zambrano, E. [Endocrine disruptor compounds and their role in the developmental programming of the reproductive axis]. *Rev. Invest. Clin.*, **2007**, *59*, 73-81.

[127] Schneider, J. E. Metabolic and hormonal control of the desire for food and sex: implications for obesity and eating disorders. *Horm. Behav.*, **2006**, *50*, 562-71.

[128] Guzman, C.; Cabrera, R.; Cardenas, M.; Larrea, F.; Nathanielsz, P. W.; Zambrano, E. Protein restriction during fetal and neonatal development in the rat alters reproductive function and accelerates reproductive ageing in female progeny. *J. Physiol.*, **2006**, *572*, 97-108.

[129] Zambrano, E.; Rodriguez-Gonzalez, G. L.; Guzman, C.; Garcia-Becerra, R.; Boeck, L.; Diaz, L.; Menjivar, M.; Larrea, F.; Nathanielsz, P. W. A maternal low protein diet during pregnancy and lactation in the rat impairs male reproductive development. *J. Physiol.*, **2005**, *563*, 275-84.

[130] Zambrano, E. [The transgenerational mechanisms in developmental programming of metabolic diseases]. *Rev. Invest. Clin.*, **2009**, *61*, 41-52.

[131] Torres, N.; Bautista, C. J.; Tovar, A. R.; Ordaz, G.; Rodriguez-Cruz, M.; Ortiz, V.; Granados, O.; Nathanielsz, P. W.; Larrea, F.; Zambrano, E. Protein restriction during pregnancy affects maternal liver lipid metabolism and fetal brain lipid composition in the rat. *Am. J. Physiol. Endocrinol. Metab.*, **2009**.

[132] Zambrano, E.; Martinez-Samayoa, P. M.; Bautista, C. J.; Deas, M.; Guillen, L.; Rodriguez-Gonzalez, G. L.; Guzman, C.; Larrea, F.; Nathanielsz, P. W. Sex differences in transgenerational alterations of growth and metabolism in progeny (F2) of female offspring (F1) of rats fed a low protein diet during pregnancy and lactation. *J. Physiol.* **2005**, *566*, 225-36.

[133] Zambrano, E.; Martinez-Samayoa, P. M.; Rodriguez-Gonzalez, G. L.; Nathanielsz, P. W. Dietary intervention prior to pregnancy reverses metabolic programming in male offspring of obese rats. *J. Physiol.*, *588*, 1791-9.

[134] Reyes-Castro, L. A.; Rodriguez, J. S.; Rodriguez-Gonzalez, G. L.; Wimmer, R. D.; McDonald, T. J.; Larrea, F.; Nathanielsz, P. W.; Zambrano, E. Pre- and/or postnatal protein restriction in rats impairs learning and motivation in male offspring. *Int. J. Dev. Neurosci.*, *29*, 177-82.

[135] Reyes-Castro, L. A.; Rodriguez, J. S.; Rodriguez-González, G. L.; Chavira, R.; Bautista C, C. J.; McDonald, T. J.; Nathanielsz, P. W.; Zambrano, E. Pre and/or postnatal protein restriction developmentally programs affect and risk assessment behaviors in adult male rats. *Behav. Brain, Res.*, **2011**, In Press.

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