

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Role of Leptin in the Reproduction and Metabolism: Focus on Regulation by Seasonality in Animals

Malgorzata Szczesna and Dorota A. Zieba
*University of Agriculture in Krakow
 Poland*

1. Introduction

The hypothesis of the existence of a peripheral factor that provides the brain with information on energy status was first proposed in the 1950s (Kennedy, 1953). This hypothesis formed the basis for further investigations that eventually led to the characterization of the obese (*ob/ob*) mouse, a homozygous mutant that lacks a critical factor for the regulation of body weight (Friedman & Halaas, 1998).

This key element of the system regulating food intake has proven to be leptin, a protein hormone produced in adipose tissue. The concentration of this hormone in the blood provides an organism with information about its nutritional status and energy reserves. Leptin acts on hunger and satiety centers in the hypothalamus that affect the regulation of appetite (Halaas et al., 1995). This hormone's activity has primarily been observed in the central nervous system, especially within various parts of the hypothalamus and hypothalamic nuclei. Leptin activity was confirmed in the arcuate nucleus (ARC), ventro-medial hypothalamus (VMH), dorso-medial hypothalamus (DMH), mammillary nuclei, lateral hypothalamic area (LHA) and preoptic area (POA) by Elmquist and colleagues (1998), Williams and colleagues (1999) and Morgan & Mercer (2001). In peripheral tissues, leptin directly stimulates lipolysis and inhibits lipogenesis. Direct effects of leptin were also observed in pancreatic β cells, indicating effects on the regulation of glucose homeostasis independent of the central nervous system (Kieffer et al., 1997; Zieba et al., 2003) and suggesting that leptin may affect energy balance in various ways.

The metabolic status of an organism, which is defined in part by the availability of energy and nutrients to tissues, influences almost all biological functions. Among these functions, reproductive capacity is one of the most important. In linking energy homeostasis to feeding behavior and procreative functions, leptin plays a crucial role in the regulation of reproductive processes, acting at all levels of the gonadotropic axis. Additionally, apart from the mechanisms of energy homeostasis and regulation of reproduction, where leptin plays relatively well-known roles, this protein is also an important regulator of neuroendocrine functions (Wauters et al., 2000). Its impact has been observed on different levels of hormonal axes, ranging from releasing hormone secretion from the hypothalamus and influencing pituitary hormone secretion to a direct influence on the secretory activity of peripheral tissues.

2. Leptin is a potent regulator of energy homeostasis

Leptin receptor expression occurs at the highest levels in the ARC, which is known to affect appetite regulation (Elmquist et al., 1999). There are two main types of neurons with opposite effects. Activation of the orexigenic neurons, which produce neurotransmitters such as neuropeptide Y (NPY) and agouti-related peptide (AgRP), stimulates the appetite and decreases metabolism, while activation of anorectic neurons leads to the release of such factors as proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which reduce the consumption of food (Morgan & Mercer, 2001). When an organism's energy reserves that are stored in adipose tissue decrease and serum leptin concentration is reduced, NPY/AgRP neurons are activated, and POMC neurons are inhibited, stimulating the organism to acquire and store energy. These neurons have also been implicated in transducing the action of leptin on GnRH neuronal activity and are sensitive to negative energy balances (Lin et al., 2000).

2.1 Leptin and the leptin receptor

Leptin is a non-glycosylated polypeptide with a molecular mass of approximately 16 kDa encoded by the *ob* gene (*Obese Gene*; Zhang et al., 1994). The leptin gene is highly conserved across species, and it is located on chromosome 7q31.3 in humans (Green et al., 1995) and on chromosome 4q32 in cattle (Stone et al., 1996). This gene's DNA sequence includes more than 15,000 base pairs and contains 3 exons, which are separated by 2 introns (Green et al., 1995). The mouse protein exhibits 83% homology with human leptin (Zhang et al., 1994), and both share many structural similarities with other members of the helical cytokine family, including interleukin-6 (IL-6), prolactin (PRL) and growth hormone (GH) (Zhang et al., 1997). Leptin is synthesized as a pro-hormone (167 amino acids) and released into the bloodstream following the cleavage of a signaling segment (21 amino acids) in the form of a hormone 146 amino acids in length (Prolo et al., 1998; Zhang et al., 1994).

Although adipose tissue is the primary source of leptin, the production of leptin has been observed in a variety of other tissues, including the stomach (Sobhani et al., 2000), skeletal muscle (J. Wang, 1998), fetal cartilage (Hoggard et al., 1998), pituitary tissue (Jin et al., 1999), mammary tissue (Smith-Kirwin et al., 1998), and placenta (Masuzaki et al., 1997). Leptin may be found in the bloodstream in its free form or complexed with leptin-binding proteins, and this characteristic appears to be species-specific (Garcia et al., 2002; Houseknecht et al., 1996). In humans, the half-life of free leptin is approximately 30 min (Trayhurn et al., 1999), with the kidneys being responsible for approximately 80% of leptin clearance from the peripheral circulation (Meyer et al., 1997). Additionally, leptin secretion follows a circadian rhythm (Licinio et al., 1998b), with a nadir early in the morning (0800–0900 h), an increase during the day, and a peak between 2400 and 0200 h.

The multitude of organs in which the presence of leptin receptors has been identified confirms the pleiotropic character of leptin's action. Expression of the *db* gene (*Diabetes Gene*), which encodes a leptin receptor (Tartaglia et al., 1995) has been confirmed within pituitary (Iqbal et al., 2000), adipose tissue in sheep (Dyer et al., 1997), on the granulosa, theca and interstitial cells of the ovary (Karlsson et al., 1997), in testis (Caprio et al., 1999), and in heart, liver, lung, kidney, adrenal gland (Hoggard et al., 1997), small intestine and lymph nodes.

The leptin receptor has a single membrane-spanning domain and exists in different isoforms (Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, Ob-Re and Ob-Rf) derived from alternative splicing of its

mRNA (Bjorbaek et al., 1997). All isoforms have similar ligand-binding domains but differ at the C-terminus in the intracellular domain. The Ob-Rb isoform, which contains a long intracellular domain, is the only one with both of the protein motifs necessary for activation of the Janus kinase 2 and signal transducers and activators of transcription (JAK-STAT) pathway (Uotani et al., 1999). The leptin receptor lacks intrinsic enzymatic activity and mediates signals through the activation of receptor-associated intracellular JAKs. The leptin receptor homodimerizes upon ligand binding and activates JAK/STAT pathways. Phosphorylated STATs dimerize and then translocate to the nucleus, where they bind to DNA and affect target gene transcription (Banks et al., 2000). This system can be modulated by a large variety of cellular factors. Although the JAK2/STAT3 pathway has been considered the major signaling mechanism activated by the leptin receptor, mitogen-activated protein kinase (MAPK) (Niswender et al., 2001) and phosphatidylinositol-3 kinase (PI-3 K) (Niswender et al., 2001) have also been implicated in leptin receptor signaling.

2.2 Factors influencing the synthesis and secretion of leptin

The concentration of leptin circulating in the bloodstream depends primarily on the amount of the protein stored in body fat deposits, and this relationship presents a positive correlation (Maffei et al., 1995). The levels of leptin mRNA are variable in different adipose tissue depots, suggesting that there are site-specific variations in the expression of the leptin gene (Maffei et al., 1995). In humans, leptin expression in subcutaneous fat is higher than in other kinds of adipose tissue (Montague et al., 1997), while in rats, the highest level of leptin mRNA is observed in internal fat depots, especially in perirenal and epididymal adipose tissue (Maffei et al., 1995; Trayhurn et al., 1995).

The expression level of leptin is also dependent on age (Rayner et al., 1997) and sex (Montague et al., 1997). Sexual dimorphism involves not only the level of leptin mRNA expression but also the correlation between the mass of adipose tissue and the concentration of the hormone. The concentration of leptin circulating in the blood is 2 to 3 times higher in women than in men. Additionally, female synthesis of leptin in relation to body weight is not only approximately 75% higher, but leptin is also much more easily released from adipose tissue in females (Licinio et al., 1998a). It has been suggested that these observed differences may be partly due to the impact of sex hormones.

Changes in leptin concentrations are dependent on age and physiological state. In premenopausal women, the plasma concentrations of leptin are higher than in postmenopausal individuals (Rosenbaum et al., 1996). Higher levels of this protein are also noted in women of procreative age, and the concentration of leptin increases with the maturation of ovarian follicles in the menstrual cycle. Moreover, its concentration is higher in the luteal phase compared with the follicular phase of the ovarian cycle (Popovic & Casanueva, 2002). In cattle, however, the concentration of leptin decreases in the luteal phase and early follicular phase (G.L. Williams et al., 2002).

Pregnancy and lactation are important factors that determine the amount of leptin in the bloodstream. Interestingly, hyperleptinemia occurring during pregnancy is not associated with a reduction in food intake, which suggests that this state induces a kind of leptin resistance. In sheep, the concentration of leptin in the bloodstream increases during the first half of pregnancy (Ehrhardt et al., 2001) and depends on the number of fetuses, presenting higher values in the case of a multiple pregnancy (Kulcsar et al., 2006). The concentration of leptin is reduced in the second half of pregnancy, and a low concentration of this hormone is maintained during the first weeks of lactation (Ehrhardt et al., 2001). Lactation significantly

reduces the expression of leptin mRNA in adipose tissue, and the concentration of this protein in the bloodstream is approximately five times lower in lactating compared with non-lactating ewes (Sorensen et al., 2002).

Nutritional status also has an impact on the concentration of leptin in the blood. Undernutrition, or even short-term restriction of access to food, results in a significant reduction in leptin concentrations in ruminants (Amstalden et al., 2000), rodents (Trayhurn et al., 1995) and humans (Boden et al., 1996).

Photoperiod can also affect leptin expression in numerous species, including sheep. Exposure of ovariectomized adult ewes to a long day length for 4-6 weeks stimulated leptin release and expression in perirenal adipose tissue, and this effect was independent of any change in the number of adipocytes or feed intake (Bocquier et al., 1998). A similar effect of long days on leptin expression was previously reported in Syberian hamster (*Phodopus sungorus*) (Klingenspor et al., 1996). In lactating dairy cows, exposure to different photoperiodic conditions significantly affects the gene expression of leptin and its receptors in adipose tissue. Cows exposed to long-day conditions (18:6) exhibited higher expression of leptin compared with cows housed under neutral (12:12) or short day-length (6:18) conditions. Additionally, expression of the long form of the leptin receptor (*Ob-Rb*) was found to be downregulated by short-day conditions (Bernabucci et al., 2006). Bertolucci and co-workers (2005) demonstrated the circadian rhythms of leptin release from adipose tissue in sheep, with a minimum concentration of the hormone occurring during the light phase and peak secretion being observed during the dark phase. Moreover, the amplitude of these changes was higher during the short days (Marie et al., 2001). Diurnal variations in circulating leptin concentrations have also been reported in humans (Licinio et al., 1998b). The mechanisms involved in photoperiod-induced differences in adipose tissue leptin expression remain unknown. Direct effects of the sympathetic nervous system and interactions between melatonin and PRL have been suggested to play a role in this process. In the membranes of adipocytes, there are many receptors mediating the sensitivity of adipose tissue to various hormonal factors. For example, on mammalian adipocytes, it has been observed that receptors for leptin (Dyer et al., 1997), insulin (Jarett et al., 1980), melatonin (Alonso-Vale et al., 2005; Zalatan et al., 2001), PRL (Ling et al., 2000) and GH (Carter-Su et al., 1984) are present, suggesting that these hormones may directly regulate the activity of adipocytes, including their secretory activity.

2.3 State of leptin resistance

Although it was originally referred to as an *anti-obesity* hormone in humans, leptin's effects are counteracted in some individuals by a natural resistance associated with hyperleptinemia, which is related to changes in hypothalamic sensitivity to leptin associated with, for example, pregnancy and lactation, malnutrition or obesity. In sheep, it was observed that the hypothalamus is resistant to leptin in some periods, and this phenomenon is related to the adaptation of these animals to annual changes in energy supply and demand (Marie et al., 2001). During the long-day season, the concentration of leptin in blood plasma increases by 180% compared with during the short-day season (Marie et al., 2001), but this is not associated with the anorectic action of leptin. During this period, when there is an abundance of food and it is readily accessible, sheep exhibit increased appetite and appear to be insensitive to high concentrations of leptin (resulting from increased adiposity). Seasonal leptin resistance allows these animals to live in a changing climate and store energy that they will be able to use in periods of reduced food availability. In autumn and

winter, sheep exhibit sensitivity to leptin at the physiological level, and their appetite adjusts approximately to their nutritional status. This paradox can be explained by the state of leptin resistance or leptin insensitivity occurring during long days, but the neuroendocrinal basis of this phenomenon remains unknown. Suggestions that hypothalamic sensitivity to the anorexic effects of leptin in sheep changes in a seasonally dependent manner were confirmed in studies using exogenous leptin (Miller et al., 2002). The amount of food intake was found to be affected by exogenous leptin only during a period of days of decreasing length, while in the spring, this response was not observed (Miller et al., 2002).

Changes during the year related to leptin sensitivity have been observed in other seasonal animal species. In Siberian hamsters, the potency of exogenous leptin in reducing food intake is significantly more marked in periods of short days than during long days (Atcha et al., 2000; Klingenspor et al., 2000). These observations provide insight into the phenomenon of seasonal changes in sensitivity to leptin, not only in relation to the regulation of food intake, but also related to the modifying effects of season on other leptin-induced responses.

It appears that an intracellular protein induced by leptin receptor activation, suppressor of cytokine signaling-3 (SOCS-3), may mediate leptin resistance at the molecular level, mainly within the region of the arcuate nucleus, as it effectively blocks leptin signaling (Bjorbaek et al., 2000). Uotani and colleagues (1999) suggest the desensitization of leptin receptors as the cause of reduced sensitivity, and El-Haschimi & Lehnert (2003) suggest disturbances in the transport of the hormone across the blood-brain barrier. Leptin resistance is probably not caused by a single mechanism but, rather, results from a combination of the above-mentioned factors. However, the critical mechanism(s) underlying this process remain unclear.

3. Seasonality of leptin action

In the last decade, many factors affecting the appetite and energy expenditure have been described. It has been shown that the effects of many of these factors are dependent on photoperiod. Melatonin, which is a biochemical indicator of changes in light conditions, is functionally and anatomically involved in the modulation of numerous interactions linked with adaption to changes in food intake according to circadian and annual changes in the environment. Moreover, many other hormones involved in maintaining energy homeostasis are characterized by daily and annual fluctuations of their concentrations in the bloodstream. In temperate latitudes, sheep are seasonal breeders for which reproductive activity is controlled mainly by photoperiod. Nocturnal secretion of pineal-derived melatonin provides information about day length, but neither the target sites for its action in the brain nor the neuropeptide circuits engaged by the melatonin signal are well defined (Adam & Mercer, 2004). Recently, attention has been focused on the role of leptin, in this process, which is strongly implicated as one of the major peripheral signals controlling body fat reserves and appetite in mammals.

In numerous animal species, food intake and the amount of fat stored change over the annual cycle. Melatonin can affect adipose tissue through sympathetic innervation. The presence of neurons projecting directly into fat tissue from suprachiasmatic nuclei (SCN), which are structures in the brain that are particularly rich in melatonin receptors, has been observed (Bartness et al., 2001), which was confirmed by experiments carried out on the Siberian hamster. Infusion of melatonin to the SCN caused a reduction in fat mass analogous to the reduction observed during short days (Bartness et al., 1993).

Furthermore, receptors for melatonin have been found in the DMH and anterior hypothalamic area, but not in the ARC, in seasonal species (Morgan & Mercer, 1994). The ARC theoretically rule out the possibility of direct effects of melatonin on leptin signaling within the ARC, which is the primary site of leptin receptors in brain. Colocalization of these receptors elsewhere has not yet been demonstrated; however, both melatonin and leptin receptors have been independently localized to the DMN. Morgan et Mercer (2001) reported that neurons from the DMH, SCN, and ARC project to the paraventricular nucleus (PVN). Adam & Mercer (2004) proposed that melatonin could contribute to hypothalamic sensitivity to leptin through acting on the PVN region (the center of appetite regulation), with the PVN thus representing a site at which melatonin and leptin feedback may be coordinated. Relative leptin insensitivity during long days (LD) may be necessary to prevent the observed increase in leptin concentrations, which would cause appetite reduction and thereby counteract photoperiod-driven increases in voluntary food intake and body weight (Tups et al., 2004). Collectively, these observations imply that there is a distinct system of regulation in which normal responses to leptin and energy deficits are overridden by photoperiod (Tups et al., 2004).

In addition to the indirect effects of melatonin, which occur through the nervous system, melatonin may directly modulate the activity of adipose tissue via the endocrine system by acting on specific receptors on membranes of adipocytes. In isolated rat adipocytes, melatonin inhibits basal and insulin-induced lipogenesis (Ng & Wong, 1986). These observations were confirmed in studies by Zalatan and colleagues (2001), in which melatonin inhibited isoproterenol-induced lipolysis, and this effect was blocked by pertussis toxin and a melatonin receptor agonist. Moreover, effects of melatonin were demonstrated only in the case of adipocytes derived from adipose tissue taken from the groin area, but not the epididymal region, suggesting a site-specific nature of these interactions (Zalatan et al., 2001). Melatonin was observed to enhance leptin expression in primary cultures of rat adipocytes in the presence of insulin; this effect was blocked by pertussis toxins and forskolin, which are known to be selective antagonists of the melatonin receptor (Alonso-Vale et al., 2005). This type of stimulation was promoted when melatonin was added in a circadian-like manner (12 h + / 12 h -; Alonso-Vale et al., 2006).

The role of melatonin in leptin secretion is still poorly understood. Several authors have reported that melatonin reduces the leptin concentration in the blood, while authors have reported an opposite tendency. The removal of the pineal gland in rats was associated with an elevated concentration of leptin circulating in the bloodstream, and the application of exogenous melatonin reversed this effect (Canpolat et al., 2001). Other studies indicate that intraperitoneal injection of exogenous melatonin (1 mg) did not affect the secretion of leptin in rats when it was administered during the day; however, it slightly reduced the leptin concentration at night (Mastronardi et al., 2000). Exogenous melatonin reduced the levels of leptin in Siberian hamsters (*Mesocricetus auratus*) (Korhonen et al., 2008). In Syrian hamsters, high levels of melatonin in the blood were associated with a decrease in leptin concentrations, and the removal of the pineal gland resulted in increases in the leptin level (Gunduz, 2002). In contrast, in seasonally breeding mink (*Mustela vison*), melatonin implantation in the fall was linked to a stimulating effect on leptin in the bloodstream (Mustonen et al., 2000). Similarly, these hormones exhibited positive relationships with circadian rhythms in sheep (Bertolucci et al., 2005). However, regarding seasonal rhythms, the pattern observed for leptin concentrations is the opposite of that found for the release of melatonin.

Interestingly, there are also several reports indicating that leptin can affect melatonin secretion. It has been shown that recombinant ovine leptin is able to modulate melatonin release in ovine pineal gland explants *in vitro*, and this effect is seasonally dependent (Zieba et al., 2007). Exogenous leptin inhibits the secretion of melatonin from pineal gland explants during LD and stimulates this process during short days (SD) (Zieba et al., 2007). A seasonal switch in the sensitivity of the ovine pineal gland to leptin was also reported based on *in vivo* studies in sheep. Following intracerebroventricular (icv) infusion of leptin, stimulatory effects on melatonin secretion during SD and inhibitory effects during LD were observed (Zieba et al., 2008).

4. SOCS-3 as a negative regulator of leptin signaling

SOCS-3 is a potent inhibitor of the JAK/STAT signaling pathway, negatively regulating the signal transduction of a variety of factors, including leptin. Despite the fact that proteins currently classified as SOCS were identified and characterized as negative regulators of cytokine signaling in the late twentieth century (Endo et al., 1997; Naka et al., 1997; Starr et al., 1997), their role in the coordination of hormonal interactions is still poorly understood. In physiological conditions, the expression of SOCS mRNA in the majority of tissues, with the exception of the brain, is rather low. However, it is known that some specific factors (cytokines, growth factors, hormones) can rapidly alter the level of SOCS expression.

Leptin supplied through intraperitoneal or intravenous injection was found to result in a significant increase of SOCS-3 expression in numerous hypothalamic nuclei in male *ob/ob* mice (Bjorbaek et al., 1998). A lack of changes in SOCS-3 mRNA levels in mice without functional leptin receptors (*db/db*) confirms that this process is associated with the activation of leptin receptors (Bjorbaek et al., 1998). Additionally, *in vitro* studies on hamster ovary cell lines have confirmed that leptin induces SOCS-3 mRNA transcription and protein expression (Bjorbaek et al., 1999). Moreover, these investigators demonstrated that increases in the SOCS-3 level caused by preincubation in the presence of leptin were linked to leptin resistance during sequent incubation.

Localization of this protein in the hypothalamic nucleus and the wide variety of factors that are able to induce its expression suggest that SOCS-3 may play a pivotal role in the modulation of neuroendocrinal interactions. Additionally, there is evidence implying that SOCS-3 has an important function within the pituitary. Recent experiments indicate that the SOCS-3 expression level is also dependent on environmental factors, such as photoperiodic conditions and nutritional status.

4.1 The role of SOCS-3 in seasonal leptin resistance

If the major control of seasonal changes in leptin sensitivity takes place at the hypothalamic level, the question arises as to how this effect is mediated. Although several potential mechanisms to account for this process have been proposed (Levin et al., 2004; Münzberg et al., 2005), the one receiving the most attention has been the inhibition of intracellular leptin signaling by SOCS-3.

Studies in the Siberian hamster (Tups et al., 2004) have demonstrated that reduced SOCS-3 activity during short day period contributes to increased sensitivity to leptin and that, conversely, increased activity of SOCS-3 signaling contributes to the relative leptin insensitivity seen in LD. Moreover, leptin was able to induce SOCS-3 expression exclusively in short days and had no effect during long days, which indicates that this

interaction is also seasonally dependent (Adam & Mercer, 2004; Tups et al., 2004). Changes in hypothalamic sensitivity to leptin at different times of the year have previously been reported in sheep (Adam et al., 2003; Miller et al., 2002). However, these studies mainly investigated the photoperiodic regulation of appetite and reproductive axes.

Studies conducted by the authors of the present paper indicated that intracerebroventricular leptin infusions were also able to alter hypothalamic SOCS-3 expression in sheep. However, this effect was observed only during long day', but not during short day', conditions (Zieba et al., 2008), while in the pituitary, leptin affects this expression only during short days (Szczesna et al., 2011). This explains the existence of leptin resistance in the hypothalamus with simultaneous maintenance of leptin sensitivity in the pituitary. Seasonally dependent changes in the responsiveness of the ovine hypothalamus to leptin have also been reported (Miller et al., 2002). This may be the result of increased levels of SOCS-3 expression and, to some extent, may explain the phenomenon of a lack of sensitivity of the hypothalamus with respect to the anorexic effects of leptin in the long day season.

One of the key reports presenting the results of experiments on changes in the expression of SOCS-3 factors in response to annual environmental rhythms was produced by Tups and colleagues (2004). Based on studies in the Siberian hamster, these investigators described the changes in SOCS-3 mRNA levels in response to short-term fasting and long-term dietary restrictions and the effects of exogenous leptin relative to short (8 h light: 16 h darkness)- and long (16 h light: 8 h dark)-day conditions. The authors showed that the expression of SOCS-3 in the ARC was significantly higher during long days than during short days in all of the experimental systems studied (Tups et al., 2004). It was found that leptin administered through intraperitoneal injections (2 mg/kg BW) significantly increased the expression of SOCS-3 factors in the ARC in animals kept in short-day conditions, without changing the expression in individuals remaining under the influence of a long day (Tups et al., 2004). The lack of an effect of leptin during LD observed in these experiments could result from a high endogenous photoperiod-induced SOCS-3 level, which, in turn, led to the occurrence of leptin resistance.

Based on the wide range of factors affecting SOCS-3 expression and the large number of potential interactions occurring in organisms, the impact of other hormones on the modulation of endocrine relationships (also relative to the season) should not be neglected. Presumably, during LD, at least in hamsters, the SOCS-3 gene is expressed constitutively at a high rate, regardless of the level of endogenous leptin (Tups et al., 2004), and it is very possible that maintaining a high level of SOCS-3 results from interactions other than with leptin.

The complexity of this issue may underlie the results of studies on the daily fluctuations in SOCS-3 expression. In rats, which are characterized by nocturnal increases of activity, including in relation to food intake and increased levels of leptin secretion during the dark phase, the mRNA expression of SOCS-3 is much lower at night than during the day (Denis et al., 2004). However, studies on daily changes in the expression of SOCS-3 in the hypothalamus of Siberian hamsters found no correlation between the time of day and the level of SOCS-3 mRNA, as its expression remained at comparable levels in the light and dark phases (Ellis et al., 2008). In relation to other genes involved in the regulation of energy balance, diurnal variations in expression level were observed only in the case of leptin receptor mRNA, for which the level increased in the dark phase, but only in a long day photoperiod (Ellis et al., 2008). This indicates that depending on the season, hypothalamic sensitivity to leptin may be regulated by several mechanisms simultaneously.

Taking into account that melatonin is the main cue of changes in day length, pineal hormone or other hormones for which the concentration in the bloodstream is highly dependent on the concentration of melatonin (for example, PRL) may be involved in the seasonally dependent modulation of the expression of SOCS-3. It is possible that the differences observed between seasons with respect to when exogenous leptin can influence the expression of SOCS-3 in the hypothalamus that were observed in hamsters (Tups et al., 2004) and sheep (Zieba et al., 2008) resulted from the action of other hormones (steroids) associated with differences in the timing of seasonal reproduction activity in these species.

4.2 SOCS-3 and obesity

It is believed that changes in the expression of SOCS-3 factors are also associated with pathological states of insensitivity to cytokines, as in the case of obesity. In rats with experimentally induced obesity (initiated by lesions in the VMH or the administration of a high-fat diet), the expression of these factors in adipose tissue was significantly increased (Z. Wang et al., 2000). Particularly interesting information regarding the role of SOCS-3 in the induction of leptin resistance has been provided by research on mice in which the SOCS-3 gene was specifically knocked-out (Mori et al., 2004). Total absence of the SOCS-3 gene is lethal in the early stages of fetal life because of the numerous disturbances that occur, for example, in the development of the placenta (Roberts et al., 2001) or in erythropoiesis (Marine et al., 1999). Based on these findings, Mori and colleagues (2004) carried out studies using two animal models in which deletions in the SOCS-3 gene occurred exclusively in nerve tissue. Leptin infusions were not associated with increased levels of SOCS-3 factors within the hypothalamus, a characteristic of individuals with a wild-type genotype, and the observed reduction in food consumption and body weight was significantly higher in both experimental models compared with control subjects with normal genes (Mori et al., 2004). Through analysis of the impact of obesity and high-fat diet-induced leptin resistance, it was also found that while wild animals are susceptible to the occurrence of both of these phenomena, individuals with the SOCS-3 deficient are more resistant to weight gain (Mori et al., 2004). Similar conclusions were drawn based on research conducted on mice with an SOCS-3 +/- genotype with haploinsufficiency of SOCS-3 (Howard et al., 2004). Other studies have found that the lethal yellow mouse (Ay/a), characterized by obesity, hyperleptinemia and leptin resistance, presents significantly elevated levels of SOCS-3 mRNA compared with wild-type individuals (Bjorbaek et al., 1998). However, experiments conducted by Emilsson and colleagues (1999) demonstrated that the basal expression of SOCS-3 mRNA in the hypothalamus is higher in obese animals lacking the genes encoding leptin (*ob/ob*) compared to wild-type individuals. This suggests that, at least in this case, expression of SOCS-3 mRNA was not caused by leptin but by other factors associated with obesity, once again indicating the role of those suppressors in integrating of the activities of various factors.

Because of the wide range of actions and strong biological activity of leptin, the effects of its action must be strictly controlled to prevent disadvantageous consequences of excessive stimulation of leptin receptors. Localization of SOCS-3 mRNA in neurons of the hypothalamus and a significant induction of their expression in response to numerous factors indicates that SOCS-3 plays a crucial role in cytokine-induced regulation of neuroendocrine interactions. The observations presented above suggest that SOCS-3 proteins are important regulators playing a key role in feeding-induced or genetic-origin

obesity and leptin resistance, leading to the hypothesis that therapy consisting of a reduction in the levels of these proteins within the hypothalamus might be helpful in treating obesity associated with reduced sensitivity to leptin.

5. Leptin and reproduction

Leptin also plays a crucial role in the regulation of reproductive processes. It is generally accepted that there is a close relationship between reproductive processes and nutritional status. There is some evidence that leptin is one of the pivotal factors modulating these processes (Sahu, 2003). Exogenous leptin accelerates entry into a period of sexual maturity of female rodents, including mice (Ahima et al., 1997) and rats (Cheung et al., 1997). High levels of endogenous leptin, associated with excess body fat, are responsible for the earlier occurrence of first menstruation in girls who are overweight compared with lean girls at the same age (Jaruratanasirikul et al., 1997).

Malnutrition has a negative impact on reproductive processes, ranging from a reduction in libido to negative effects on pregnancy (implantation disorders, increased fetal resorption, abortion) and the inhibition of ovulation. Nutritional deprivation of females, whether as a result of an insufficient supply of energy in the diet or excessive demands for energy (e.g., lactation), inhibits GnRH release, leading to reduced secretion of LH and even to anovulation and anestrus (Scaramuzzi & Martin, 2008). Both chronic undernutrition and acute fasting with associated hypoglycemia quickly lead to suppression of the GnRH system and a cessation of LH pulsatility in monogastric species (Bronson, 1988). In contrast, stimulation by leptin of the hypothalamic-gonadotropic axis by ruminant species is observed predominantly in animals and tissues pre-exposed to an intense negative energy balance (Zieba et al., 2003).

The hypothalamic GnRH pulse generator in ruminant species (cattle, sheep and goats) is much less sensitive to nutritional deprivation due to the fact that ruminant species derive metabolizable energy primarily from volatile fatty acid production in the rumen. Therefore, both serious and chronic food restrictions are required to result in negative reproductive consequences in adults. Importantly, the central reproductive axis of pre-pubertal ruminants is much more sensitive to nutritional perturbations, such as acute fasting, than that of sexually mature individuals (Zieba et al., 2005). It was demonstrated that short-term fasting (48-72 h) is sufficient to suppress the frequency of LH pulses in peripubertal heifers (Amstalden et al., 2000). Moreover, treatment with exogenous leptin prevented these decreases, implying a direct action of leptin at the hypothalamic level (Maciel et al., 2004a). In contrast, mature cows subjected to similar feeding restrictions, resulting in analogous metabolic responses to those seen peripubertal heifers (e.g., decreased leptin mRNA expression in adipose tissue, decreased plasma concentrations of leptin, insulin and IGF-1), did not exhibit a decrease in the pulsatile secretion of LH (Maciel et al., 2004b). However, similar to the heifers, mature cows subjected to short-term fasting became intensely hypersensitive to exogenous leptin. Intravenous infusion of leptin in this animal model promptly increased baseline and overall mean concentrations of LH and markedly augmented the amplitude of individual pulses of LH (Amstalden et al., 2000). Studies conducted by Nonaka and co-workers (2005) have provided clear evidence demonstrating a direct effect of leptin on LH release from primary cultured anterior pituitary cells collected from fully fed steers.

Although leptin's action on GnRH neuronal activity was confirmed in several studies, the neuroendocrine mechanisms associated with this process remain unclear. Although few

GnRH neurons, if any, have been found to express the leptin receptors in the rat (Zamorano et al., 1997) and monkey (Finn et al., 1998), leptin has been found to stimulate the release of GnRH from rat and porcine hypothalamic explants and from hypothalamus of cattle during *in vivo* study (Zieba et al., 2005). Expression of leptin receptor mRNA has been demonstrated in both the anterior pituitary gland and hypothalamus (Amstalden et al., 2002), and the leptin receptors has been identified within regions rich in GnRH neurons, such as the ARC, the medial preoptic area, and the median eminence (Ahima et al., 2000; Sahu, 2003), and *in vitro* studies using explants collected from normally fed rodents indicate that leptin can act directly at both sites (Amstalden et al., 2002; Watanobe, 2002) to stimulate the release of GnRH and LH, respectively. Data from Watanobe (2002) strongly suggest that leptin could act at both the cell bodies and axon terminals of GnRH neurons to stimulate the release of the neurohormone *in vivo*, with greater sensitivity of the ARC to leptin observed in fasted than in fed rats. Based upon increases in both receptor mRNA and protein levels (Baskin et al., 1998, 1999), fasting may enhance the leptin receptor concentration in the ARC. Similarly, the expression of the full-length leptin receptor, both in the ventromedial hypothalamus and in the pituitary gland, was found to be much greater in feed-restricted ewes than in ewes that were well fed (Dyer et al., 1997), which in turn suggests that dietary restriction can increase the sensitivity of both of these tissues to the action of leptin. In castrated yearling rams subjected to 72 h of food deprivation, leptin restores pulsatile LH secretion, although direct leptin action is not sufficient to influence LH release in satiated animals (Nagatani et al., 2000). In properly nourished ovariectomized ewes, icv infusion of leptin did not affect LH secretion, although the dose of leptin used was sufficient to reduce food intake (Henry et al., 1999), while in long-term food-restricted animals, leptin partially restores LH release without affecting appetite (Henry et al., 2001). In prepubertal female lambs, central (Morrison et al., 2001) and intravenous (Morrison et al., 2002) infusion of leptin did not affect LH release in either well-fed or undernourished animals, despite the fact that LH pulse frequencies were lower in diet-restricted than fed animals (Morrison et al., 2001).

The discrepancies linked with the observations mentioned above may be connected with the influence of the different times of year in which the studies were carried out, as seasonally dependent changes in sensitivity to leptin have been reported in sheep. It was shown that in spring, icv infusions of leptin in castrated, adequately nourished rams cause a significant increase in LH secretion compared with the results obtained when the infusions were performed in the fall (Miller et al., 2002). In turn, Adam et al. (2003) observed that a single, pharmacological icv dose of leptin in sheep specifically stimulated the frequency of LH pulses and simultaneously decreased appetite in late autumn. In contrast, no effect was observed when leptin was applied to the same sheep in the spring. However, the latest results from this group (Adam et al., 2006) do not support the hypothesis that leptin stimulates the reproductive neuroendocrine axis under the influence of photoperiod, although photoperiod modulates intrahypothalamic leptin sensitivity related to appetite. These observations in sheep concerning voluntary feed intake and the lack of effects observed on the GnRH/LH system are consistent with similar studies in Siberian hamsters, which are resistant to leptin during the long days but become responsive to leptin treatment in terms of body weight and abdominal fat loss during the short days (Atcha et al., 2000).

An influence of leptin is also observed in the peripheral sites of the reproductive axis. Additionally, leptin exhibits direct action within the ovary, including inhibition of estradiol secretion from ovarian follicles (Spicer & Francisco, 1997), thus participating in the

regulation of the growth and maturation of this organ. Placental leptin, acting by paracrine and autocrine mechanisms, appears to be involved in the modulation of maternal-fetal interactions, including angiogenesis and the processes of growth and metabolism within the fetus and the uterus (Ashworth et al., 2000).

6. *Pas de trois*: leptin, ghrelin and orexin interaction

In addition to the previously described effects of leptin, the growing interest in the regulation of both metabolic and reproductive function has led to increased interest in orexin A and B, produced in the hypothalamus (De Lecea et al., 1998; Sakurai et al., 1999), and ghrelin, produced mainly in the stomach (Kojima et al., 1999).

The LHA is one of the sites that mediates the orexigenic properties of ghrelin (Cowley et al., 2003). As an integrator of ghrelin-derived input, the lateral hypothalamus acts as part of a larger feeding-related network that includes the PVN, ARC, and DMH. Ghrelin receptors are present in hypothalamic NPY/AgRP neurons, and ghrelin activates those neurons to stimulate food intake. It was observed that the mRNA levels of ghrelin in the stomach, hypothalamus and pituitary gland increase significantly during starvation. Furthermore, it was found that changes in the level of ghrelin in plasma are correlated with the level of leptin (Cummings & Foster, 2003). During fasting, plasma ghrelin concentrations increase, with a simultaneous decrease in leptin concentrations, and during feeding, the situation is reversed. Moreover ghrelin, activates the neurons of the ARC in a dose-dependent manner, whereas leptin inhibits these neurons. To emphasize the close relationship that exists between leptin and ghrelin in the regulation of energy, appetite and body weight, Cummings and Foster (2003) used the term “ghrelin-leptin tango”, which accurately describes the nature of the interaction between these hormones. Kim et al. (2004) demonstrated that long-term intracerebellar or intraventricular administration of leptin reduced the levels of glucose and insulin, decreased food intake by 39% and reduced body fat weight by 41%, while co-administration of ghrelin nullified these effects. Barazzoni et al. (2003) demonstrated that leptin functions as an adiposity signal to negatively regulate ghrelin concentrations in the rat.

Interestingly, there are several pieces of evidence indicating that some of ghrelin's actions are under the influence of photoperiod. Central infusions of ghrelin, depending on the season, stimulated food intake, modulated the secretion of GH and inhibited the release of GnRH/LH in castrated rams (Harrison et al., 2008). Injections of ghrelin into the third ventricle of the brain caused a temporary increase in food intake during long days, with no similar effect seen during short days. In turn, inhibition of the release of GnRH/LH was observed only when ghrelin was administered in short days during the breeding season of sheep. Furthermore, it has been demonstrated that in the rat, exogenous melatonin decreases ghrelin concentration (Mustonen et al., 2001). In turn, Brunetti et al. (2002) showed that ghrelin inhibits the melatonin precursor serotonin in the rat hypothalamus. Studies conducted in sheep indicate a lack of any effect of day length on ghrelin-treated pineal gland explants in relation to melatonin concentration (Zieba et al., 2011). It is noteworthy that the length of day had no effect on circadian or annual concentrations of endogenous ghrelin in sheep. However, during both seasons – long and short days, ghrelin decreased melatonin concentrations when administered at either low or high doses (Harrison et al., 2008).

In analyzing the interactions between leptin and ghrelin, the finding of greatest interest is that opposite effects of their actions are found not only in relation to the regulation of food

intake, but also to the season in which adjustments in food intake occur. During short days, injections of leptin inhibit appetite (Miller et al., 2002), while centrally administered ghrelin has no effect on food intake (Harrison et al., 2008). Intriguing results were obtained by Zieba and co-workers (2011) through *in vitro* studies on ovine pineal glands. They showed that the addition of leptin to ghrelin-treated cultures increased melatonin concentrations compared to cultures supplemented with ghrelin alone during both long and short photoperiods. Although leptin decreased melatonin secretion during long days (Zieba et al., 2007), leptin and ghrelin acted synergistically to increase melatonin concentration to higher levels than in either individually-treated or untreated cultures (Zieba et al., 2011). These findings contribute to the formation of hypotheses concerning the joint action of leptin and ghrelin in the regulation of energy homeostasis depending on photoperiod.

Among the orexygenic peptides, orexins (also known as hypocretins) have also attracted considerable attention in recent years. Studies in rats have shown that exogenous administration of orexins increases food intake (Sakurai et al., 1998). Subsequently, other functions of these proteins were confirmed in studies demonstrating their role in the regulation of sleep-wake rhythms (Chemelli et al., 1999). Despite the fact that orexin-containing neurons represent a relatively small group of cells, it has been proven that their projections are spread through many parts of the central nervous system. Experimental data indicate the involvement of these proteins in various regulatory processes. Recent studies suggest that orexins play important roles as neurotransmitters within the central nervous system, and the orexins involved in this system may represent a link between the hypothalamus and other parts of the brain. It was found incontrovertibly that the expression of orexin receptors (OxR1 and OxR2) is not confined to the area of the hypothalamus, though it is the strongest in this region. The largest quantity of OxR1 mRNA was detected in the VMH. Additionally, it OxR1 mRNA was located in the lateral and posterior hypothalamus, POA, hippocampus and in the pituitary and the pineal gland. In turn, the highest expression of hypothalamic OxR2 mRNA was found in the PVN. Studies conducted in 2000 by Date and co-workers confirmed that there is strong expression of OxR1 and OxR2 mRNA in the middle, anterior (glandular) and posterior (neural) lobes of the pituitary gland of the rat. It has been shown that in sheep, orexin gene expression varies depending on the length of day: levels are higher during short days compared to long days (Archer et al., 2002). Moreover, prepro-orexin mRNA and orexin immunoreactivity display diurnal variation in the hypothalamic area, supporting the involvement of this hypothalamic peptide in the daily rhythm of melatonin synthesis (Archer et al., 2002).

Furthermore, orexin neurons are anatomically linked to components of the circadian system and innervate the pineal gland directly via a central input, but they may also be a part of the multineuronal pathway culminating in noradrenergic input from the superior cervical ganglion (Mikkelsen et al., 2001). They demonstrated that through its receptors present in the pineal gland, orexin (mainly B) decreases melatonin releases and reduces the activation of N-acetyltransferase, which is a key enzyme involved in the synthesis of pineal hormone. Studies carried out on explants of ovine pineal glands (Zieba et al., 2011) demonstrated a dose-dependent orexin stimulatory effect on melatonin release, mainly during the long photoperiod, with a lower dose having a stronger effect. No such effect was observed during short photoperiod, whereas a decrease in melatonin release was noted, as described by Mikkelsen et al. (2001), in cultured rat pinealocytes treated with orexin B. Hakansson and co-workers (1999) confirmed the presence of leptin receptor immunoreactivities in orexin neurons of the lateral hypothalamus. Therefore, it is possible that leptin can modulate food intake and reproduction via an interaction with the activity of orexin neurons.

Interesting links are also found between ghrelin and orexins. Intraventricular injections of ghrelin demonstrated anatomical and functional synaptic connections between neurons secreting orexins and ghrelin in the region of the lateral hypothalamus (Toshinai et al., 2003). Injections of ghrelin induced an immediate expression of C-Fos protein, which is the marker of neuronal activity in the neurons synthesizing orexin (Toshinai et al., 2003).

Taking into account the role of ghrelin and orexins in the regulation of energy homeostasis, it is not surprising that, as in the case of leptin, both ghrelin and orexin affect processes associated with reproduction. Intraventricular injections of orexin in ovariectomized female rats were associated with a decrease in LH pulse frequency (Tamura et al., 1999). Orexin A was also found to be an inhibitor of LH release from the pituitaries of female rats by Russell et al. (2001). Kohsaka et al. (2001) indicate the involvement of this peptide in the regulation of the pre-ovulatory output of LH and PRL in rats. They showed that administration of orexin to fasted animals can lead to a return of the concentrations of these hormones to the state observed prior to food restriction. Additionally, anti-orexin sera completely abolish the flow of both hormones in normally fed rats (Kohsaka et al., 2001). Studies on mammals have demonstrated that ghrelin is able to suppress pulsatile LH secretion in a different species. However, in castrated rams, the effect of exogenous ghrelin on the release of GnRH/LH has been shown only during the short day period (Harrison et al., 2008). Acetylated ghrelin inhibited spontaneous LH pulsatility and the LH response to naloxone (Lanfranco et al., 2008). It was also provided, that ghrelin decreased GnRH release by hypothalamic explants *in vitro*, so its action for inhibitory effects on the gonadotropic release take place also in a higher level of this axis (Fernandez-Fernandez et al., 2005a). Ogata et al. (2009) provided that suppressive effect of central injection of ghrelin on pulsatile LH secretion was mediated by β -endorphin which suppressed pulsatile GnRH secretion from hypothalamus. In turn, studies conducted on goldfish pituitary cells indicate that ghrelin may also stimulate LH release via mechanism linked with Ca^{2+} entry and voltage-sensitive Ca^{2+} channels (Grey et al., 2010). Expression of ghrelin gene and gene of ghrelin receptor was reported also on gonadal stage – in the testis (Barreiro et al., 2003) and in the ovary (Camino et al., 2003). It was also suggested that elevated ghrelin levels may be a negative modifier for embryo implantation (Kawamura et al., 2003) and development (Fernandez-Fernandez et al., 2005b) during pregnancy.

Taken together, these findings indicate an abundance of functions performed by proteins engaged in the regulation of energy homeostasis, in which these proteins form a close web of interactions and interrelationships. Based on these results, we can compare this relationship not to a tango of two partners, as suggested by Cummings and Foster, but rather to a *Pas de trois* – a dance of three, where not only leptin and ghrelin, but also orexin play very important roles. In this dance, there is a place for individual variations in each of these players, but their joint actions play the primary role. Due to the complexity of these interactions, as in a *Pas de trois*, this dance is spectacular and technically difficult, and the dancers exhibit a masterly precision and grace.

7. Conclusion

Intense research has been carried out to provide explanations for the relationships between hormones engaged in the regulation of energy homeostasis, metabolism and reproduction resulting from the importance of these interactions and the processes controlled by them. These studies have been conducted not only in theoretical, but also in practical terms, for the

treatment of pathological phenomena associated with endocrine dysfunction in humans and animals or related to the economic viability of farming. Because of their strictly regulated adaptation to environmental conditions related to the plasticity of their endocrine system, as well as the presence of physiological leptin resistance, sheep represent a particularly interesting model for such studies. The observations described above emphasize the close relationship that exists between photoperiod, which is a powerful factor that influences the course of many processes in sheep, its main biochemical indicator, melatonin, and peptides involved in the regulation of energy homeostasis.

8. Acknowledgment

This work was supported by a grant from the Polish National Research Council (MNiSW NN 311 318436)

9. References

- Adam, CL., Archer, ZA. & Miller, DW. (2003). Leptin actions on the reproductive neuroendocrine axis in sheep. *Reproduction. Supplement*, Vol.61, pp. 283-297, ISSN 1477-0415
- Adam, CL. & Mercer, JG. (2004). Appetite regulation and seasonality: implications for obesity. *The Proceedings of the Nutrition Society*, Vol.63, No.3, pp. 413-419, ISSN 0029-6651
- Adam, CL., Findlay, PA. & Miller, DW. (2006). Blood-brain leptin transport and appetite and reproductive neuroendocrine responses to intracerebroventricular leptin injection in sheep: influence of photoperiod. *Endocrinology*, Vol.147, No.10, pp. 4589-4598, ISSN 0013-7227
- Ahima, RS., Dushay, J., Flier, SN., Prabakaran, D. & Flier, JS. (1997). Leptin accelerates the onset of puberty in normal female mice. *Journal of Clinical Investigation*, Vol.99, No.3, pp. 391-395, ISSN 0021-9738
- Ahima, RS., Saper, CB., Flier, JS. & Elmquist, JK. (2000). Leptin regulation of neuroendocrine systems. *Frontiers in Neuroendocrinology*, Vol.21, No.3, pp. 263-307, ISSN 0091-3022
- Alonso-Vale, MIC., Andreotti, S., Peres, SB., Anhe, GF., Borges-Silva, CN., Cipolla-Neto, J. & Lima, FB. (2005). Melatonin enhances leptin expression by rat adipocytes in the presence of insulin. *American Journal of Physiology. Endocrinology and Metabolism*, Vol.288, No.4, pp. 805-812, ISSN 0193-1849
- Alonso-Vale, MIC., Andreotti, S., Borges-Silva, CN., Mukai, PY., Cipolla-Neto, J. & Lima, FB. (2006). Intermittent and rhythmic exposure to melatonin in primary cultured adipocytes enhances the insulin and dexamethasone effects on leptin expression. *Journal of Pineal Research*, Vol.41, No.1, pp. 28-34, ISSN 0742-3098
- Amstalden, M., Garcia, MR., Williams, SW., Stanko, RL., Nizielski, SE., Morrison, CD., Keisler, DH. & Williams, GL. (2000). Leptin gene expression, circulating leptin, and luteinizing hormone pulsatility are acutely responsive to short-term fasting in prepubertal heifers: relationships to circulating insulin and insulin-like growth factor I. *Biology of Reproduction*, Vol.63, No.1, pp. 127-133, ISSN 0006-3363
- Amstalden, M., Garcia, MR., Stanko, RL., Nizielski, SE., Morrison, CD., Keisler, DH. & Williams, GL. (2002). Central infusion of recombinant ovine leptin normalizes plasma insulin and stimulates a novel hypersecretion of luteinizing hormone after

- short-term fasting in mature beef cows. *Biology of Reproduction*, Vol.66, No.5, pp. 1555-1561, ISSN 0006-3363
- Archer, Z.A., Findlay, P.A., Rhind, S.M., Mercer, J.G. & Adam, C.L. (2002). Orexin gene expression and regulation by photoperiod in the sheep hypothalamus. *Regulatory Peptides*, Vol.104, No.1-3, pp. 41-45, ISSN 0167-0115
- Ashworth, C.J., Hoggard, N., Thomas, L., Mercer, J.G., Wallace, J.M. & Lea, R.G. (2000). Placental leptin. *Reviews of Reproduction*, Vol.5, No.1, pp. 18-24, ISSN 1359-6004
- Atcha, Z., Cagampang, F.R., Stirland, J.A., Morris, I.D., Brooks, A.N., Ebling, F.J., Klingenspor, M. & Loudon, A.S. (2000). Leptin acts on metabolism in a photoperiod-dependent manner, but has no effect on reproductive function in the seasonally breeding Siberian hamster (*Phodopus sungorus*). *Endocrinology*, Vol.141, No.11, 4128-4135, ISSN 0013-7227
- Banks, A.S., Davis, S.M., Bates, S.H. & Myers Jr., M.G. (2000). Activation of downstream signals by the long form of the leptin receptor. *Journal of Biological Chemistry*, Vol.275, No.19, pp. 14563-14572, ISSN 0021-9258
- Barazzoni, R., Zanetti, M., Stebel, M., Biolo, G., Cattin, L. & Guarnieri, G. (2003). Hyperleptinemia prevents increased plasma ghrelin concentration during short-term moderate caloric restriction in rats. *Gastroenterology*, Vol.124, No.5, pp. 1188-1192, ISSN 0016-5085
- Barreiro, M.L., Suominen, J.S., Gaytan, F., Pinilla, L., Chopin, L.K., Casaneuva, F.F., Dieguez, C., Aguilar, C., Toppari, J. & Tena-Sempere, M. (2003). Developmental, stage-specific and hormonally regulated expression of growth hormone secretagogue receptor messenger RNA in rat testis. *Biology of Reproduction*, Vol.68, No.5, pp. 1631-1640, ISSN 0006-3363
- Bartness, T.J., Powers, J.B., Hastings, M.H., Bittman, E.L. & Goldman, B.D. (1993). The timed infusion paradigm for melatonin delivery: What has it taught us about melatonin signal, its reception, and the photoperiodic control of seasonal responses? *Journal of Pineal Research*, Vol.15, No.4, pp. 161-190, ISSN 0742-3098
- Bartness, T.J., Song, C.K. & Demas, G.E. (2001). SCN efferents to peripheral tissues: implications for biological rhythms. *Journal of Biological Rhythms*, Vol.16, No.3, pp. 196-204, ISSN 0748-7304
- Baskin, D.G., Seeley, R.J., Kuijper, J.L., Lok, S., Weigle, D.S., Erickson, J.C., Palmiter, R.D. & Schwartz, M.W. (1998). Increased expression of mRNA for the long form of the leptin receptor in the hypothalamus is associated with leptin hypersensitivity and fasting. *Diabetes*, Vol.47, No.4, pp. 538-543, ISSN 0012-1797
- Baskin, D.G., Breininger, J.F., Bonigut, S. & Miller, M.A. (1999). Leptin binding in the arcuate nucleus is increased during fasting. *Brain Research*, Vol.828, No.1-2, pp. 154-158, ISSN 0006-8993
- Bernabucci, U., Basirico, L., Lacetera, N., Morera, P., Ronchi, B., Accorsi, P.A., Seren, E. & Nardone, A. (2006). Photoperiod affects gene expression of leptin and leptin receptors in adipose tissue from lactating dairy cows. *Journal of Dairy Science*, Vol.89, No.12, pp. 4678-4686, ISSN 0022-0302
- Bertolucci, C., Caola, G., Foa, A. & Piccione, G. (2005). Daily rhythms of serum leptin in ewes: effects of feeding, pregnancy and lactation. *Chronobiology International*, Vol.22, No.5, pp. 817-827, ISSN 0742-0528

- Bjorbaek, C., Uotani, S., Da Silva, B. & Flier, JS. (1997). Divergent signaling capacities of the long and the short isoforms of the leptin receptor. *Journal of Biological Chemistry*, Vol.272, No.51, pp. 32686-32695, ISSN 0021-9258
- Bjorbaek, C., Elmquist, J., Frantz, J., Shoelson, S. & Flier, J. (1998). Identification of SOCS-3 as a potential mediator of central leptin resistance. *Molecular Cell*, Vol.1, No.4, pp. 619-625, ISSN 1097-2765
- Bjorbaek, C., El-Haschimi, K., Frantz, JD. & Flier, JS. (1999). The role of SOCS-3 in leptin signaling and leptin resistance. *Journal of Biological Chemistry*, Vol.274, No.42, pp. 30059-30065, ISSN 0021-9258
- Bjorbaek, C., Lavery, HJ. & Bates, SH. (2000). SOCS-3 mediates feedback inhibition of the leptin receptor via Tyr985. *Journal of Biological Chemistry*, Vol.275, No.51, pp. 40649-40657, ISSN 0021-9258
- Bocquier, F., Bonnet, M., Faulconnier, Y., Guerre-Millo, M., Martin, P. & Chilliard, Y. (1998). Effects of photoperiod and feeding level on perirenal adipose tissue metabolic activity and leptin synthesis in the ovariectomized ewe. *Reproduction, Nutrition, Development*, Vol.38, No.5, pp. 489-498, ISSN 0926-5287
- Boden, G., Chen, X., Mazzoli, M. & Ryan, I. (1996). Effect of fasting on serum leptin in normal human subjects. *Journal of Clinical Endocrinology and Metabolism*, Vol.81, No.9, pp. 2419-2423, ISSN 0021-972X
- Bronson, FH. (1988). Effect of food manipulation on the GnRH-LH-estradiol axis of young female rats. *The American Journal of Physiology*, Vol.254, No.4 Pt 2, pp. R616-R621, ISSN 0002-9513
- Brunetti, L., Recinella, G., Orlando, B., Michelotto, C., Di Nisio, C. & Vacca, M. (2002). Effects of ghrelin and amylin on dopamine, norepinephrine and serotonin release in the hypothalamus. *European Journal of Pharmacology*, Vol.454, no.2-3, pp. 189-192, ISSN 0014-2999
- Caminos, JE., Tena-Sempere, M., Gaytan, F., Sanchez-Criado, JE., Barreiro, ML., Nogueiras, R., Casanueva, FF., Aguilar, E. & Dieguez, C. (2003). Expression of ghrelin in the cyclic and pregnant rat ovary. *Endocrinology*, Vol.144, No.4, pp. 1594-602, ISSN 0013-7227
- Canpolat, S., Sandal, S., Yilmaz, B., Yasar, A., Kutlu, S., Baydas, G. & Kelestimur, H. (2001). Effects of pinealectomy and exogenous melatonin on serum leptin levels in male rat. *European Journal of Pharmacology*, Vol.428, No.1, pp. 145-148, ISSN 0014-2999
- Caprio, M., Isidori, AM., Carta, AR., Moretti, C., Dufau, ML. & Fabbri A. (1999). Expression of leptin receptors in rodents Leydig cells. *Endocrinology*, Vol.140, No.11, pp. 4939-4947, ISSN 0013-7227
- Carter-Su, C., Schwartz, J. & Kikuchi, G. (1984). Identification of a high-affinity growth hormone receptor in rat adipocytes. *Journal of Biological Chemistry*, Vol.259, No.2, pp.1099-1104, ISSN 0021-9258
- Chemelli, RM., Willie, JT., Sinton, CM., Elmquist, JK., Scammell, T., Lee, C., Richardson, JA., Williams, SC, Xiong, Y., Kisanuki, Y., Fitach, TE., Nakazato, M, Hammer, RE., Saper, CB. & Yanagisawa, M. (1999). Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell*, Vol.98, No.4, pp. 437-451, ISSN 0092-8674
- Cheung, CC., Thornton, JE., Kuijper, JL., Weigle, DS., Clifton, DK. & Steiner, RA. (1997). Leptin is metabolic gate for the onset of puberty in the female rat. *Endocrinology*, Vol.138, No.2, pp. 855-858, ISSN 0013-7227

- Chilliard, Y., Delavaud, C. & Bonnet, M. (2005). Leptin expression in ruminants: nutritional and physiological regulations in relation with energy metabolism. *Domestic Animal Endocrinology*, Vol.29, No.1, pp. 3-22, ISSN 0739-7240
- Cowley, MA., Smith, RG., Diano, S., Tschöp, M., Pronchuk, N., Grove, KL., Strasburger, CJ., Bidlingmaier, M., Esterman, M., Heiman, ML., Garcia-Segura, LM., Nillni, EA., Mendez, P., Low, MJ., Sotonyi, P., Friedman, JM., Liu, H., Pinto, S., Colmers, WF., Cone, RD. & Horvath, TL. (2003). The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. *Neuron*, Vol.37, No.4, pp. 649-661, ISSN 0896-6273
- Cummings, DE. & Foster, KE. (2003). Ghrelin-leptin tango in body-weight regulation. *Gastroenterology*, Vol.124, No.5, pp. 1532-1535, ISSN 0016-5085
- Date, Y., Mondal, MS., Matsukura, S., Ueta, Y., Yamashita, H., Kaiya, H., Kangawa, K. & Nakazato, M. (2000). Distribution of orexin/hypocretin in the rat median eminence and pituitary. *Brain Research. Molecular Brain Research*, Vol.76, No.1, pp. 1-6, ISSN 0169-328X
- De Lecea, L., Kilduff, TS., Peron, C., Gao, X-B., Foye, PE., Danielson, PE., Fukuhara, C., Battenberg, ELF., Gautvik, VT., Bartlett, FS., Frankel, WN., Van den Pol, AN., Bloom, FE., Gautvik, KM. & Sutcliffe, JG. (1998). The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.95, No.1, pp. 322-327, ISSN 0027-8424
- Denis, RPG., Bing, C., Brocklehurst, S., Harrold, JA., Vernon, RG. & Williams, G. (2004). Diurnal changes in hypothalamic neuropeptide and SOCS-3 expression: effects of lactation and relationship with serum leptin and food intake. *Journal of Endocrinology*, Vol.183, No.1, pp. 173-181, ISSN 0022-0795
- Dyer, CJ., Simmons, JM., Matteri, RL. & Keisler, DH. (1997). Leptin receptor mRNA is expressed in ewe anterior pituitary and adipose tissues and is differentially expressed in hypothalamic regions of well-fed and feed-restricted ewes. *Domestic Animal Endocrinology*, Vol.14, No.2, pp. 119-128, ISSN 0739-7240
- Ehrhardt, RA., Slepatis, RM., Bell, AW. & Boisclair, YR. (2001). Maternal leptin is elevated during pregnancy in sheep. *Domestic Animal Endocrinology*, Vol.21, No.2, pp. 85-96, ISSN 0739-7240
- El-Haschimi, K. & Lehnert, H. (2003). Leptin resistance - or why leptin fails to work in obesity. *Experimental and Clinical Endocrinology & Diabetes*, Vol.111, No.1, pp. 2-7, ISSN 0947-7349
- Ellis, C., Moar, KM, Logie, TJ., Ross, AW., Morgan, PJ. & Mercer, JG. (2008). Diurnal profiles of hypothalamic energy balance gene expression with photoperiod manipulation in the Siberian hamster, *Phodopus sungorus*. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, Vol.294, No.4, pp. R1148-R1153, ISSN 0363-6119
- Elmqvist, JK., Bjorbaek, C., Ahima, RS., Flier, JS. & Saper, CB. (1998). Distributions of leptin receptor mRNA isoforms in the rat brain. *Journal of Comparative Neurology*, Vol.395, No.4, pp. 535-547, ISSN 0021-9967
- Elmqvist, JK., Elias, CF. & Saper, CB. (1999). From lesions to leptin: hypothalamic control of food intake and body weight. *Neuron*, Vol.22, No.2, pp. 221-232, ISSN 0896-6273
- Emilsson, V., Jonathan, ARS, de Groot, RD., Lister, CA. & Cawthorne, MA. (1999). Leptin treatment increases suppressors of cytokine signaling in central and peripheral tissues. *FEBS Letters*, Vol.455, No.1-2, pp. 170-174, ISSN 0014-5793

- Endo, TA., Masuhara, M., Yokouchi, M., Suzuki, R., Sakamoto, H., Mitsui, K., Matsumoto, A., Tanimura, S., Ohtsubo, M., Misawa, H., Miyazaki, T., Leonor, N., Taniguchi, T., Fujita, T., Kanakura, Y., Komiya, S. & Yoshimura, A. (1997). A new protein containing an SH2 domain that inhibits JAK kinases. *Nature*, Vol.387, No.6636, pp. 921-924, ISSN 0028-0836
- Fernandez-Fernandez, R., Tena-Sempere, M., Navarro, VM., Barreiro, ML., Castellano, JM., Aguilar, E. & Pinilla, L. (2005a). Effects of ghrelin upon gonadotropin-releasing hormone and gonadotropin secretion in adult female rats: in vivo and in vitro studies. *Neuroendocrinology*, Vol.82, No.5-6, pp. 245-255, ISSN 0028-3835
- Fernandez-Fernandez, R., Navarro, VM., Barreiro, ML., Vigo, EM., Tovar, S., Sirotkin, AV., Casanueva, FF., Aguilar, E., Dieguez, C., Pinilla, L. & Tena-Sempere, M. (2005b). Effects of chronic hyperghrelinemia on puberty onset and pregnancy outcome in the rat. *Endocrinology*, Vol.146, No.7, pp. 3018-3025, ISSN 0013-7227
- Finn, PD., Cunningham, MJ., Pau, KY., Spies, HG., Clifton, DK. & Steiner, RA. (1998). The stimulatory effect of leptin on the neuroendocrine reproductive axis of the monkey. *Endocrinology*, Vol.139, No.11, pp. 4652-4662, ISSN 0013-7227
- Friedman, JM. & Halaas, JL. (1998). Leptin and the regulation of the body weight in mammals. *Nature*, Vol.395, No.6704, pp. 763-770, ISSN 0028-0836
- Garcia, MR., Amstalden, M., Williams, SW., Stanko, RL., Morrison, CD., Keisler, DH., Nizielski, SE. & Williams GL. (2002). Serum leptin and its adipose gene expression during pubertal development, the estrous cycle, and different seasons in cattle. *Journal of Animal Science*, Vol.80, No.8, pp. 2158-2167, ISSN 0021-8812
- Green, ED., Maffei, M., Braden, VV., Porencu, R., De Silva, U., Zhang, Y., Chua, SC., Leibel, R., Weissanbach, J. & Friedman, JM. (1995). The human obese (OB) gene: RNA expression pattern and mapping on the physical, cytogenic and genetic maps of chromosome 7. *Genome Research*, Vol.5, No.1, pp. 5-12, ISSN 1088-9051
- Grey, CL., Grayfer, L., Belosevic, M. & Chang, JP. (2010). Ghrelin stimulation of gonadotropin (LH) release from goldfish pituitary cells: presence of the growth hormone secretagogue receptor (GHS-R1a) and involvement of voltage-sensitive Ca²⁺ channels. *Molecular and Cellular Endocrinology*, Vol.317, No.1-2, pp. 64-77, ISSN 0303-7207
- Gunduz B. (2002). Daily rhythm in serum melatonin and leptin levels in the Syrian hamster (*Mesocricetus auratus*). *Comparative Biochemistry and Physiology. Part A, Molecular & Integrative Physiology*, Vol.132, No.2, pp. 393-401, ISSN 1095-6433
- Hakansson, ML., de Lecea, L., Sutcliffe, JG., Yanagisawa, M. & Meister, B. (1999). Leptin receptor-abd STAT-3- immunoreactivities in hypocretin/orexin neurons of the lateral hypothalamus. *Journal of Neuroendocrinology*, Vol.11, No.8, pp. 653-663, ISSN 0953-8194
- Halaas, JL., Gajiwala, KS., Maffei, M., Cohen, SL., Chait, BT., Rabinowitz, D., Lallone, RL., Burley, SK. & Friedman, JM. (1995). Weight-reducing effects of the plasma protein encoded by the obese gene. *Science*, Vol.269, No.5223, pp. 543-546, ISSN 0193-4511
- Harrison, JL., Miller, DW., Findlay, PA. & Adam, CL. (2008). Photoperiod influences the central effects of ghrelin on food intake, GH and LH secretion in sheep. *Neuroendocrinology*, Vol.87, No.3, pp. 182-192, ISSN 0028-3835
- Henry, BA., Goding, JW., Alexander, WS., Tilbrook, AJ., Canny, BJ., Dunshea, F., Rao, A., Mansell, A. & Clarke, IJ. (1999). Central administration of leptin to ovariectomised ewes inhibits food intake without affecting the secretion of hormones from

- pituitary gland: evidence for a dissociation of effects on appetite and neuroendocrine function. *Endocrinology*, Vol.140, No.3, pp. 1175-1182, ISSN 0013-7227
- Henry, BA., Goding, JW., Tilbrook, AJ., Dunshea, F. & Clarke, IJ. (2001). Intracerebroventricular infusion of leptin elevates the secretion of luteinizing hormone without affecting food intake in long-term food-restricted sheep, but increases growth hormone irrespective of body weight. *Journal of Endocrinology*, Vol.168, No.1, pp. 67-77, ISSN 0022-0795
- Hoggard, N., Mercer, JG., Rayner, DV., Moar, K., Trayhurn, P. & Williams, LM. (1997). Localization of leptin receptor mRNA splice variants in murine peripheral tissues by RT-PCR and in situ hybridization. *Biochemical and Biophysical Research Communications*, Vol.232, No.2, pp. 383-387, ISSN 0006-291X
- Hoggard, N., Hunter, L., Trayhurn, P., Williams, LM. & Mercer JG. (1998). Leptin and reproduction. *The Proceedings of the Nutrition Society*, Vol.57, No.3, pp. 421-427, ISSN 0029-6651
- Houseknecht, KL., Mantzoros, CS., Kuliawat, R., Hadro, E., Flier, JS. & Kahn, BB. (1996). Evidence for leptin binding to proteins in serum of rodents and humans: modulation with obesity. *Diabetes*, Vol.45, No.11, pp. 1638-1643, ISSN 0012-1797
- Howard, JK., Cave, BJ., Oksanen, LJ., Tzamelis, I., Bjorbaek, C. & Flier, JS. (2004). Enhanced leptin sensitivity an attenuation of diet-induced obesity in mice with haploinsufficiency of Socs3. *Nature Medicine*, Vol.10, No.7, pp. 739-743, ISSN 1078-8956
- Iqbal, J., Pompolo, S., Considine, RV. & Clarke, IJ. (2000). Localization of leptin receptor-like immunoreactivity in the corticotropes, somatotropes, and gonadotropes in the ovine anterior pituitary. *Endocrinology*, Vol.141, No.4, pp. 1515-1520, ISSN 0013-7227
- Jarett, L., Schweitzer, JB. & Smith, RM. (1980). Insulin receptors: differences in structural organization on adipocyte and liver plasma membranes. *Science*, Vol.210, No.4474, pp. 1127-1128, ISSN 0193-4511
- Jaruratanasirikul, S., Mo-Suwan, L. & Lebel, L. (1997). Growth pattern and age at menarche of obese girls in a transitional society. *Journal of Pediatric Endocrinology & Metabolism*, Vol.10, No.5, pp. 487-490, ISSN 0334-018X
- Jin, L., Burguera, BG., Couce, ME., Scheithauer, BW., Lamsan, J., Eberhardt, NL., Kulig, E. & Lloyd, RV. (1999). Leptin and leptin receptor expression in normal and neoplastic human pituitary: evidence of a regulatory role for leptin on pituitary cell proliferation. *Journal of Clinical Endocrinology and Metabolism*, Vol.84, No.8, pp. 2903-2911, ISSN 0021-972X
- Karlsson, C., Lindell, K., Svensson, E., Bergh, C., Lind, P., Billig, H., Carlsson, LM. & Carlsson, B. (1997). Expression of functional leptin receptors in human ovary. *Journal of Clinical Endocrinology & Metabolism*, Vol.82, No.12, pp. 4144-4148, ISSN 0021-972X
- Kawamura, K., Sato, N., Fukuda, J., Kodama, H., Kumagai, J., Tanikawa, H., Nakamura, A., Honda, Y., Sato, T. & Tanaka, T. (2003). Ghrelin inhibits the development of mouse preimplantation embryos in vitro. *Endocrinology*, Vol.144, No.6, pp. 2623-2633, ISSN 0013-7227
- Kennedy, GC. (1953). The role of depot fat in the hypothalamic control of food intake in the rat. *Proceedings of the Royal Society of London, Series B, Biological Sciences*, Vol.140, No.901, pp. 579-592, ISSN 0080-4649

- Kieffer, T.J., Heller, R.S., Lech, C.A., Holz, G.G. & Habaner, J.F. (1997). Leptin suppression of insulin secretion by activation of ATP-sensitive K channels in pancreatic beta-cells. *Diabetes*, Vol.46, No.6, pp. 1087-1093, ISSN 0012-1797
- Kim, M.S., Namkoong, C., Kim, H.S., Jang, P.G., Kim Pak, Y.M., Katakami, H., Park, J.Y. & Lee, K.U. (2004). Chronic central administration of ghrelin reverses the effects of leptin. *International Journal of Obesity and Related Metabolic Disorders*, Vol.28, No.10, pp. 1264-1271, ISSN 0307-0565
- Klingenspor, M., Dickopp, A., Heldmaier, G. & Klaus, S. (1996). Short photoperiod reduces leptin gene expression in white and brown adipose tissue of Djungarian hamsters. *FEBS Letters*, Vol.399, No.3, pp. 290-294, ISSN 0014-5793
- Klingenspor, M., Niggemann, H. & Heldmaier, G. (2000). Modulation of leptin sensitivity by short photoperiod acclimation in the Djungarian hamster, *Phodopus sungorus*. *Journal of Comparative Physiology. Biochemical, Systemic, and Environmental Physiology*, Vol.170, No.1, pp. 37-43, ISSN 0174-1578
- Kohsaka, A., Watanobe, H., Kakizaki, Y., Suda, T., Schiöth, H.B. (2001). A significant participation of orexin-A, a potent orexigenic peptide, in the preovulatory luteinizing hormone and prolactin surges in the rat. *Brain Research*, Vol.898, No.1, pp.166-170, ISSN 0006-8993
- Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsumoto, H. & Kangawa, K. (1999). Ghrelin is a growth hormone-releasing acylated peptide from stomach. *Nature*, Vol.402, No. 6762, pp. 656-660, ISSN 0028-0836
- Korhonen, T., Mustonen, A.M., Nieminen, P. & Saarela, S. (2008). Effects of cold exposure, exogenous melatonin and short-day treatment on the weight-regulation and body temperature of the Siberian hamster (*Phodopus sungorus*). *Regulatory Peptides*, Vol.149, No.1-3, pp. 60-66, ISSN 0167-0115
- Kulcsar, M., Danko, G., Magdy, H.G.I., Reiczigel, J., Forgach, T., Prohaczik, A., Delavaud, C., Magyar, K., Chilliard, Y., Solti, L. & Huszenicza, G. (2006). Pregnancy stage and number of fetuses may influence maternal plasma leptin in ewes. *Acta Veterinaria Hungarica*, Vol.54, No.2, pp. 221-234, ISSN 0236-6290
- Lanfranco, F., Bonelli, L., Baldi, M., Me, E., Broglio, F. & Ghigo, E. (2008). Acylated ghrelin inhibits spontaneous luteinizing hormone pulsatility and responsiveness to naloxone but not that to gonadotropin-releasing hormone in young men: evidence for a central inhibitory action of ghrelin on the gonadal axis. *Journal of Clinical Endocrinology and Metabolism*, Vol.93, No.9, pp. 3633-3639, ISSN 0021-972X
- Levin, B.E., Dunn-Meynell, A.A. & Banks, W.A. (2004). Obesity-prone rats have normal blood-brain barrier transport but defective central leptin signaling before obesity onset. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, Vol.286, No.1, pp. 143-150, ISSN 0363-6119
- Licinio, J., Negrao, A.B., Mantzoros, C., Kaklamani, V., Wong, M-L., Bongiorno, P.B., Negro, P., Mulla, A., Veldhuis, J., Cernal, L., Flier, J. & Gold, P. (1998a). Sex differences in circulating human leptin pulse amplitude: clinical implications. *Journal of Clinical Endocrinology and Metabolism*, Vol.83, No.11, pp. 4140-4147, ISSN 0021-972X
- Licinio, J., Negrao, A.B., Mantzoros, C., Kaklamani, V., Wong, M., Bongiorno, P.B., Mull, A., Cernal, L., Veldhuis, J.D., Flier, J.S., McCann, S.M. & Gold, P.W. (1998b). Synchronicity of frequently sampled 24-h concentrations of circulating leptin, luteinizing hormone, and estradiol in healthy women. *Proceedings of the National*

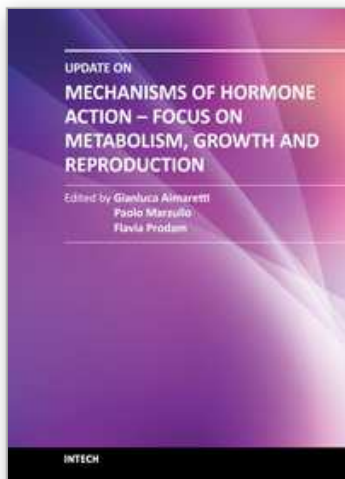
- Academy of Sciences of the United States of America*, Vol.95, No.5, pp. 2541-2546, ISSN 0027-8424
- Lin, J., Barb, CR., Matteri, RL., Kraeling, RR., Chen, X., Meinersmann, RJ. & Rampacek, GB. (2000). Long form leptin receptor mRNA expression in the brain, pituitary, and other tissues in the pig. *Domestic Animal Endocrinology*, Vol.19, No.1, pp. 53-61, ISSN 0739-7240
- Ling, C., Hellgren, G., Gebre-Medhin, M., Dillner, K., Wennbo, H., Carlsson, B. & Billig, H. (2000). Prolactin receptor gene expression in mouse adipose tissue: increases during lactation and in PRL-transgenic mice. *Endocrinology*, Vol.141, No.10, pp. 3564-3572, ISSN 0013-7227
- Maciel, MN., Zieba, DA., Amstalden, M., Keisler, DH., Neves, JP. & Williams, GL. (2004a). Chronic administration of recombinant ovine leptin in growing beef heifers: effects on secretion of LH, metabolic hormones, and timing of puberty. *Journal of Animal Science*, Vol.82, No.10, pp. 2930-2936, ISSN 0021-8812
- Maciel, MN., Zieba, DA., Amstalden, M., Keisler, DH., Neves, JP., Williams & GL. (2004b). Leptin prevents fasting-mediated reductions in pulsatile secretion of luteinizing hormone and enhances its gonadotropin-releasing hormone-mediated release in heifers. *Biology of Reproduction*, Vol.70, No.1, pp. 229-35, ISSN 0006-3363
- Maffei, M., Halaas, J., Ravussin, E., Pratley, RE., Lee, GH., Zhang, Y., Fei, H., Kim, S., Lallone R., Ranganathan, S., Kern, PA. & Friedman, JM. (1995). Leptin levels in human and rodent: measurement of plasma leptin and *ob* RNA in obese and weight-reduced subjects. *Nature Medicine*, Vol.1, No.11, pp. 1155-1161, ISSN 1078-8956
- Marie, M., Findlay, PA., Thomas, L. & Adam, CL. (2001). Daily patterns of plasma leptin in sheep: effect of photoperiod and food intake. *Journal of Endocrinology*, Vol.170, No.1, pp. 277-286, ISSN 0022-0795
- Marine, JC., McKay, C., Wang, D., Topham, DJ., Parganas, E., Nakajima, H., Pendeville, H., Yasukawa, H., Sasaki, A., Yoshimura, A., Ihle, JN. (1999). SOCS3 is essential in the regulation of fetal liver erythropoiesis. *Cell*, Vol.98, No.5, pp. 617-627, ISSN 0092-8674
- Mastronardi, CA., Walczewska, A., Yu, WH., Karanth, S., Parlow, A.F. & McCann, S.M. (2000). The possible role of prolactin in the circadian rhythm of leptin secretion in male rats. *Proceedings of The Society for Experimental Biology and Medicine*, Vol.224, No.3, pp. 152-158, ISSN 0037-9727
- Masuzaki, H., Ogawa, Y., Ssie, N., Satoh, N., Okazaki, T., Shigemoto, M., Mori, K., Tamura, N., Hosoda, K., Yoshimasa, Y., Jingami, H., Kawada, T. & Nakao, K. (1995). Human obese gene expression: adipocyte-specific expression and regional differences in the adipose tissue. *Diabetes*, Vol.44, No.7, pp. 855-858, ISSN 0012-1797
- Masuzaki, H., Ogawa, Y., Sagawa, N., Hosoda, K., Matsumoto, T., Mise, H., Nishimura, H., Yoshimasa, Y., Tanaka, I., Mori, T. & Nakao, K. (1997). Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans, *Nature Medicine*, Vol.3, No.9, pp. 1029-1033, ISSN 1078-8956
- Meyer, C., Robson, D., Rackovsky, N., Nadkarni, V. & Gerisch, J. (1997). Role of the kidney in human leptin metabolism. *The American Journal of Physiology*, Vol.273, No.5Pt1, pp. E903-E907, ISSN 0002-9513
- Mikkelsen, JD., Hauser, F., deLecea, L., Sutcliffe, JG., Kilduff, TS., Calgari, C., Pévet, P. & Simonneaux, V. (2001). Hypocretin (orexin) in the rat pineal gland: a central transmitter with effects on noradrenaline-induced release of melatonin. *European Journal of Neuroscience*, Vol.14, No.3, pp. 419-25, ISSN 0953-816X

- Miller, DW., Findlay, PA., Morrison, MA., Raver, N. & Adam, CL. (2002). Seasonal and dose-dependent effects of intracerebroventricular leptin on LH secretion and appetite in sheep. *Journal of Endocrinology*, Vol.175, No.2, pp. 395-404, ISSN 0022-0795
- Montague, CT., Prins, JB., Sanders, L., Digby, JE. & O'Rahilly, S. (1997). Depot- and sex-specific differences in human leptin mRNA expression: implications for the control of regional fat distribution. *Diabetes*, Vol.46, No.3, pp. 342-347, ISSN 0012-1797
- Morgan, PJ. & Mercer, JG. (1994). Control of seasonality by melatonin. *The Proceedings of the Nutrition Society*, Vol.53, No.3, pp. 483-93, ISSN 0029-6651
- Morgan, PJ. & Mercer, JG. (2001). The regulation of body weigh: lessons from the seasonal animals. *The Proceedings of the Nutrition Society*, Vol.60, No.1, pp. 127-134, ISSN 0029-6651
- Mori, H., Hanada, R., Hanada, T., Aki, D., Mashima, R., Nishinakamura, H., Torisu, T., Chien, KR., Yasukawa, H. & Yoshimura, A. (2004). Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. *Nature Medicine*, Vol.10, No.7, pp. 739-743, ISSN 1078-8956
- Morrison, CD., Daniel, JA., Holmberg, BJ., Djiane, J., Raver, N., Gertler, A. & Keisler, DH. (2001). Central infusion of leptin into well-fed and undernourished ewe lambs: effects on feed intake and serum concentrations of growth hormone and luteinizing hormone. *Journal of Endocrinology*, Vol.168, No.2, pp. 317-324, ISSN 0022-0795
- Morrison, CD., Wood, R., McFadin, EL., Whitley, NC. & Keisler, DH. (2002). Effect of intravenous infusion of recombinant ovine leptin on feed intake and serum concentrations of GH, LH, insulin, IGF-I, cortisol and thyroxine in growing prepubertal ewe lambs. *Domestic Animal Endocrinology*, Vol.22, No.2, pp. 103-112, ISSN 0739-740
- Münzberg, H., Bjornholm, M., Bates, SH. & Meyers Jr, MG. (2005). Leptin receptor action and mechanism of leptin resistance. *Cellular and Molecular Life Science*, Vol.62, No.6, pp. 642-652, ISSN 1420-682X
- Mustonen, AM., Nieminen, P., Hyvarinen, H. & Asikainen, J. (2000). Exogenous melatonin elevates the plasma leptin and thyroxine concentrations of the mink (*Mustela vison*). *Zeitschrift für Naturforschung. C, Journal of Biosciences*, Vol.55, No.9-10, pp. 806-813, ISSN 0939-5075
- Mustonen, AM., Nieminen, P. & Hyvarinen, H. (2001). Preliminary evidence that pharmacological melatonin treatment decreases rat ghrelin levels. *Endocrine*, Vol.16, No.1, pp. 43-46, ISSN 1355-008X
- Nagatani, S., Zeng, Y., Keisler, DH., Foster, DL., Jaffe & CA. (2000). Leptin regulates pulsatile luteinizing hormone and growth hormone secretion in sheep. *Endocrinology*, Vol.141, No.11, pp. 3965-3975, ISSN 0013-7227
- Naka, T., Narazaki, M., Hirata, M., Matsumoto, T., Minamoto, S., Aono, A., Nishimoto, N., Kajita, T., Taga, T., Yoshizaki, K., Akira, S. & Kishimoto T. (1997). Structure and function of a new STAT-induced STAT inhibitor. *Nature*, Vol.387, No.6636, pp. 924-929, ISSN 0028-0836
- Ng, TB. & Wong, CM. (1986). Effects of pineal indoles and arginine vasotocin on lipolysis and lipogenesis in isolated adipocytes. *Journal of Pineal Research*, Vol.3, No.1, pp. 55-66, ISSN 0742-3098
- Niswender, KD., Morton, GJ., Stearns, WH., Rhodes, CJ., Myers, Jr. MG. & Schwartz MW. (2001). Intracellular signaling. Key enzyme in leptin-induced anorexia. *Nature*, Vol.413, No.6858, pp. 794-795, ISSN 0028-0836

- Nonaka, S., Hashizume, T. & Kasuya, E. (2005). Effects of leptin on the release of luteinizing hormone, growth hormone and prolactin from cultured bovine anterior pituitary cells. *Animal Science Journal*, Vol.76, pp. 435-440, ISSN 1344-3941
- Ogata, R., Matsuzaki, T., Iwasa, T., Kiyokawa, M., Tanaka, N., Kuwahara, A., Yasui, T. & Irahara, M. (2009). Hypothalamic Ghrelin suppresses pulsatile secretion of luteinizing hormone via beta-endorphin in ovariectomized rats. *Neuroendocrinology*, Vol.90, No.4, pp. 364-370, ISSN 0028-3835
- Popovic, VD. & Casanueva, FF. (2002). Leptin, nutrition and reproduction: new insights. *Hormones*, Vol.1, No.4, pp. 204-217, ISSN 1109-3099
- Prolo, P., Wong, M-L. & Licinio, J. (1998). Leptin. *International Journal of Biochemistry and Cell Biology*, Vol.30, No.12, pp. 1285-1290, ISSN 1357-2725
- Rayner, DV., Dalglish, GD., Duncan, JS., Hardie, LJ., Hoggard, N. & Trayhurn, P. (1997). Postnatal development of the *ob* gene system: elevated leptin levels in suckling *fa/fa* rats. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, Vol.273, No.1-2, pp. R446-R450, ISSN 0363-6119
- Roberts, AW., Robb, L., Rakar, S., Hartley, L., Cluse, L., Nicola, NA., Metcalf, D., Hilton, DJ. & Alexander, W.S. (2001). Placental defects and embryonic lethality in mice lacking suppressor of cytokine signaling 3. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.98, No.16, pp. 9324-9329, ISSN 0027-8424
- Rosenbaum, D., Nicolson, M., Hirsch, J., Heymsfield, SB., Gallagher, D., Chu, F., Leibel, RL. (1996). Effects of gender, body composition, and menopause on plasma concentrations of leptin. *Journal of Clinical Endocrinology and Metabolism*, Vol.81, No.9, pp. 3424-3427, ISSN 0021-972X
- Russell, SH., Small, CJ., Kennedy, AR., Stanley, SA., Seth, A., Murphy, KG., Teheri, S., Ghatei, MA. & Bloom, SR. (2001). Orexin A interactions in the hypothalamo-pituitary gonadal axis. *Endocrinology*, Vol.142, No.12, pp. 5294-5302, ISSN 0013-7227
- Sahu, A. (2003). Leptin signaling in the hypothalamus: emphasis on energy homeostasis and leptin resistance. *Frontiers in Neuroendocrinology*, Vol.24, No.4, pp. 225-253, ISSN 0091-3022
- Sakurai, T., Moriguchi, T., Furuya, K., Kajiwara, N., Nakamura, T., Yanagisawa, M. & Goto, K. (1999). Structure and function of human prepro-orexin gene. *Journal of Biological Chemistry*, Vol.274, No.25, pp. 17771-17776, ISSN 0021-9258
- Scaramuzzi, RJ. & Martin, GB. (2008). The importance of interactions among nutrition, seasonality and socio-sexual factors in the development of hormone-free methods for controlling fertility. *Reproduction in Domestic Animals*, Vol.43, Suppl.2, pp. 129-136, ISSN 0936-6768
- Smith-Kirwin, SM., O'Connor, DM., De Johnston, J., Lancey, ED., Hassink, SG. & Funanage, VL. (1998). Leptin expression in human mammary epithelial cells and breast milk. *Journal of Clinical Endocrinology and Metabolism*, Vol.83, No.5, pp. 1810-1813, ISSN 0021-972X
- Sobhani, I., Vissuzaine, C., Buyse, M., Kermorgant, S., Laigneau, JP., Attoub, S., Lahy, T., Henin, D., Mignon, M. & Lewin, MJ. (2000). Leptin secretion and leptin receptor in the human stomach. *Gut*, Vol.47, No.2, pp. 178-183, ISSN 0017-5749
- Sorensen, A., Adam, CL., Findlay, PA., Marie, M., Thomas, L., Travers, MT. & Vernon, RG. (2002). Leptin secretion and hypothalamic neuropeptide and receptor gene expression in sheep. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, Vol.282, No.4, pp. R1227-R1235, ISSN 0363-6119

- Spicer, L.J. & Francisco, C.C. (1997). The adipose obese gene product, leptin: evidence of a direct inhibitory role in ovarian function. *Endocrinology*, Vol.138, No.8, pp. 3374-3379, ISSN 0013-7227
- Starr, R., Willson, T.A., Viney, E.M., Murray, L.J., Rayner, J.R., Jenkins, B.J., Gonda, T.J., Alexander, W.S., Metcalf, D., Nicola, N.A. & Hilton, D.J. (1997). A family of cytokine-inducible inhibitors of signalling. *Nature*, Vol.387, No.6636, pp. 917-921, ISSN 0028-0836
- Stone, R.T., Kappes, S.M. & Beattie, C.W. (1996). The bovine homolog of the obese gene maps to chromosome 4. *Mammalian Genome*, Vol.7, No.5, pp. 399-400, ISSN 0938-8990
- Szczesna, M., Zieba, D.A., Klocek-Gorka, B., Misztal, T. & Stepień, E. (2011). Seasonal effects of central leptin infusion and prolactin treatment on pituitary SOCS-3 gene expression in ewes. *Journal of Endocrinology*, Vol.208, No.1, pp. 81-88, ISSN 0804-4643
- Tamura, T., Irahara, M., Tezuka, M., Kiyokawa, M. & Aono, T. (1999). Orexins, orexigenic hypothalamic neuropeptides, suppress the pulsatile secretion of luteinizing hormone in ovariectomized female rats. *Biochemical and Biophysical Research Communications*, Vol.264, No.3, pp. 759-762, ISSN 0006-291X
- Tartaglia, L.A., Dembski, M., Weng, X., Den, N., Culpepper, J., Devos, R., Richards, G.J., Campfield, L.A., Clark, F.T., Deeds, J., Muir, C., Skaner, S., Moriarty, A., Moore, K.J., Smutko, J.S., Mays, G.G., Woolf, E.A., Monero, C.A. & Tepper, R.I. (1995). Identification and expression cloning of a leptin receptor, OB-R. *Cell*, Vol.83, No.7, pp. 1263-1271, ISSN 0092-8674
- Toshinai, K., Date, Y., Murakami, N., Mitsushi, S., Muhtashan, S., Shimbara, T., Guan, J.-L., Wang, Q.-P., Funashashi, H., Sukurai, T., Shioda, S., Matsukura, S., Kangawa, K. & Nakazato, M. (2003). Ghrelin-induced food intake is mediated via the orexin pathway. *Endocrinology*, Vol.144, No.4, pp. 1506-1512, ISSN 0013-7227
- Trayhurn, P., Thomas, M.E.A., Duncan, J.S. & Rayner, D.V. (1995). Effects of fasting and refeeding on *ob* gene expression in white adipose tissue of lean and obese (*ob/ob*) mice. *FEBS Letters*, Vol.368, No.3, pp. 488-490, ISSN 0014-5793
- Trayhurn, P., Hoggard, N., Mercer, J.G. & Rayner, D.V. (1999). Leptin: fundamental aspects. *International Journal of Obesity*, Vol.23, Suppl.1, pp. 22-28, ISSN 0307-0565
- Tups, A., Ellis, C., Moar, K.M., Logie, T.J., Adam, C.L., Mercer, J.G. & Klingenspor, M. (2004). Photoperiodic regulation of leptin sensitivity in the Siberian hamster, *Phodopus sungorus*, is reflected in arcuate nucleus SOCS-3 (Suppressor of Cytokine Signaling) gene expression. *Endocrinology*, Vol.145, No.3, pp. 1185-1193, ISSN 0013-7227
- Uotani, S., Bjorbaek, C., Tornøe, J. & Flier, J.S. (1999). Functional properties of leptin receptor isoforms: Internalization and degradation of leptin and ligand-induced receptor downregulation. *Diabetes*, Vol.48, No.2, pp. 279-286, ISSN 0012-1797
- Wang, J. (1998). A Nutrient sensing pathway regulates leptin gene expression in muscle and fat. *Nature*, Vol.393, No.6686, pp. 684-688, ISSN 0028-0836
- Wang, Z., Zhou, Y.-T., Kakuma, T., Lee, Y., Kalra, S.P., Kalra, P.S., Pan, W. & Unger, R.H. (2000). Leptin resistance of adipocytes in obesity: role of suppressor of cytokine signaling. *Biochemical and Biophysical Research Communications*, Vol.277, No.1, pp. 20-26, ISSN 0006-291X
- Watanobe, H. (2002). Leptin directly acts within the hypothalamus to stimulate gonadotropin-releasing hormone secretion in vivo in rats. *Journal of Physiology*, Vol.545, No.Pt 1, pp. 255-268, ISSN 0022-3751

- Wauters, M., Considine, RV. & van Gaal, LF. (2000). Human leptin: from an adipocyte hormone to an endocrine mediator. *European Journal of Endocrinology*, Vol.143, No.3, pp. 293-311, ISSN 0804-4643
- Williams, LM., Adam, CL., Mercer, JG., Moar, KM., Slater, D., Hunter, L., Findlay, PA. & Hoggard, N. (1999). Leptin receptor and neuropeptide Y gene expression in the sheep brain. *Journal of Neuroendocrinology*, Vol.11, No.3, pp. 165-169, ISSN 0953-8194
- Williams, GL., Amstalden, M., Garcia, MR., Stanko, RL., Nizielski, SE., Morrison, CD. & Keisler, DH. (2002). Leptin and its role in the central regulation of reproduction in cattle. *Domestic Animal Endocrinology*, Vol.23, No.1-2, pp. 339-349, ISSN 0739-7240
- Zalatan, F., Krause, JA. & Blask, DE. (2001). Inhibition of isoproterenol-induced lipolysis in rat inguinal adipocytes *in vitro* by physiological melatonin *via* a receptor-mediated mechanism. *Endocrinology*, Vol.142, No.9, pp. 3783-3790, ISSN 0013-7227
- Zamorano, PL., Mahesh, VB., De Sevilla, LM., Chorch, LP., Bhat, GK. & Brann, DW. (1997). Expression and localization of the leptin receptor in endocrine and neuroendocrine tissues of the rat. *Neuroendocrinology*, Vol.65, No.3, pp. 223-228, ISSN 0028-3835
- Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L. & Friedman, JM. (1994). Positional cloning of the mouse obese gene and its human homologue. *Nature*, Vol.372, No.6505, pp. 425-432, ISSN 0028-0836
- Zhang, Y., Basinski, MB., Beals, JM., Briggs, SL., Churgaj, LM., Clawson, DK., DiMarchi, RD., Furman, TC., Hale, JE., Hsiung, HM., Schoner BE, Smith, DP., Zhang, XY., Wery, JP. & Schevitz, RW. (1997). Crystal structure of the obese protein leptin-E100. *Nature*, Vol.387, No.6629, pp. 206-209, ISSN 0028-0836
- Zieba, DA., Amstalden, M., Maciel, MN., Keisler, DH., Raver, N., Gertler, A. & Williams, GL. (2003). Divergent effects of leptin on luteinizing hormone and insulin secretion are dose dependent. *Experimental Biology and Medicine*, Vol.228, No.3, pp. 325-330, ISSN 1535-3702
- Zieba, DA., Amstalden, M. & Williams, GL. (2005). Regulatory roles of leptin in reproduction and metabolism: a comparative review. *Domestic Animal Endocrinology*, Vol.29, No.1, pp. 166-185, ISSN 0739-7240
- Zieba, DA., Klocek, B., Williams, GL., Romanowicz, K., Boligłowa, L. & Wozniak, M. (2007). *In vitro* evidence that leptin suppresses melatonin secretion during long days and stimulates its secretion during short days in seasonal breeding ewes. *Domestic Animal Endocrinology*, Vol.33, No.3, pp. 358-365, ISSN 0739-7240
- Zieba, DA., Szczesna, M., Klocek-Gorka, B., Molik, E., Misztal, T., Williams, GL., Romanowicz, K., Stepień, E., Keisler, DH. & Murawski, M. (2008). Seasonal effects of central leptin infusion on secretion of melatonin and prolactin and on SOCS-3 gene expression in ewes. *Journal of Endocrinology*, Vol.198, No.1, pp. 147-155, ISSN 0804-4643
- Zieba, DA., Kirsz, K., Molik, E., Romanowicz, K. & Wojtowicz, AK. (2011). Effects of orexigenic peptides and leptin on melatonin secretion during different photoperiods in seasonal breeding ewes. An *in vitro* study. *Domestic Animal Endocrinology*, Vol.40, No.3, pp. 139-146, ISSN 0739-7240



Update on Mechanisms of Hormone Action - Focus on Metabolism, Growth and Reproduction

Edited by Prof. Gianluca Aimaretti

ISBN 978-953-307-341-5

Hard cover, 470 pages

Publisher InTech

Published online 26, October, 2011

Published in print edition October, 2011

The purpose of the present volume is to focus on more recent aspects of the complex regulation of hormonal action, in particular in 3 different hot fields: metabolism, growth and reproduction. Modern approaches to the physiology and pathology of endocrine glands are based on cellular and molecular investigation of genes, peptide, hormones, protein cascade at different levels. In all of the chapters in the book all, or at least some, of these aspects are described in order to increase the endocrine knowledge.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Malgorzata Szczesna and Dorota A. Zieba (2011). Role of Leptin in the Reproduction and Metabolism: Focus on Regulation by Seasonality in Animals, Update on Mechanisms of Hormone Action - Focus on Metabolism, Growth and Reproduction, Prof. Gianluca Aimaretti (Ed.), ISBN: 978-953-307-341-5, InTech, Available from: <http://www.intechopen.com/books/update-on-mechanisms-of-hormone-action-focus-on-metabolism-growth-and-reproduction/role-of-leptin-in-the-reproduction-and-metabolism-focus-on-regulation-by-seasonality-in-animals>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen