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

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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.

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9. References

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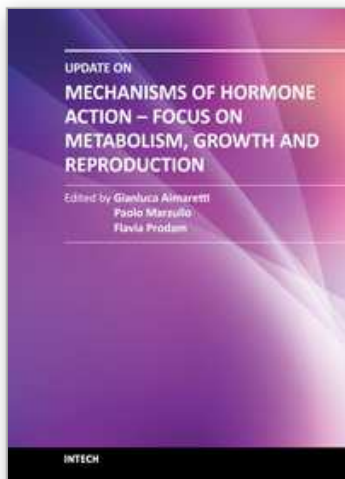
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The purpose of the present volume is to focus on more recent aspects of the complex regulation of hormonal action, in particular in 3 different hot fields: metabolism, growth and reproduction. Modern approaches to the physiology and pathology of endocrine 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.

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