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THE GONADOTROPINS SUBUNITS, *GNRH* AND GNRH RECEPTOR GENE EXPRESSION AND ROLE OF CARBON MONOXIDE IN SEASONAL BREEDING ANIMALS

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Abstract

Seasonality in reproduction occurs mainly in wild species and it is the result of natural selection. Signals to start or finish the period of reproductive activity, both environmental and hormonal depend on the neuroendocrine pathway – synthesis and secretion of pituitary hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), under the control of the hypothalamic gonadotropin-releasing hormone (GnRH) neurons. Variable frequency of GnRH pulses is not only the main factor governing primary and preovulatory release of gonadotropins, but it can also play a role in the specific transcriptional activity of gonadotropin subunit genes (*LHβ*, *FSHβ* and *Cga*). However, changes in release of GnRH pulse pattern do not explain the preferential stimulation of the synthesis and secretion of gonadotropins in the annual reproductive cycle. In this regulation also a GnRH independent mechanism participates. It seems that the main factor responsible for the occurrence of the seasonal modulation of reproduction in sheep and other mammals, is significant changes in response of GnRH systems to gonadal steroids. The effect of carbon monoxide on regulation of the hypothalamic-pituitary-gonadal axis has not been studied to date. There is substantial evidence to suggest that it may play a role in the transduction of information on day length. The presence of heme oxygenase-2 in hypothalamic areas important for regulation of pituitary secretory function and in the pituitary itself suggests that carbon monoxide, the product of this enzyme, may participate in the regulation of hormone secretion by the pineal gland.

Key words: gonadotropin gene expression, GnRH, seasonality in reproduction

Many species exhibit seasonal changes in reproductive activity but the time of parturition falls in the spring during the most favourable environmental conditions. The occurrence of annual periods of reproductive activity and reproductive silence depends on both the exogenous (environmental) and endogenous (hormonal) signals. Among many environmental variables such as temperature and food availability, photoperiod as a “constant variable” plays a dominant role in the synchronization of this activity. Species with the seasonal reproductive activity can be classified into two distinct categories: long-day breeders or short-day breeders. Representatives of the first group, which includes ferret, voles, squirrel, horse and hamster, come into breeding season after the winter solstice when the day begins to lengthen. The short-day species such as deer, wild boar, roe deer, bear, bison, goat or sheep, start their sexual activity in response to the shortening day length, i.e. late summer and early autumn. Reproductive efficiency is also reduced in pigs during the summer months. In boars, seasonal fluctuations in semen production are observed. Along with shortening day length, the ejaculate volume, total number of spermatozoa in the ejaculate and the percentage of spermatozoa motility are increasing. In the autumn and early winter there increases the level of sex hormones in the boar semen plasma and the level of testosterone in blood plasma. It is also assumed that photoperiod is a major environmental factor delaying sexual maturity of gilts during the summer time (Strzeżek, 1998).

Reproductive seasonality occurs mainly in wild species and it is the result of natural selection. Domestication and artificial selection have contributed to minimizing the effect of season on reproductive activity of animals.

Signals to start or finish the period of reproductive activity, both environmental and hormonal depend on the neuroendocrine pathway – synthesis and release of pituitary hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are under the control of the hypothalamic gonadotropin-releasing hormone (GnRH) neurons. The GnRH neuronal system plays a dominant role in the hypothalamic-pituitary-gonadal axis. Changes in the activity of GnRH neurons are crucial in the regulation of puberty and estrous cycle (Goodman et al., 1994), as well as can participate in seasonal reproductive transition.

During the reproductive silence basal concentration of LH and FSH as well as pituitary LH concentration are low and they increase gradually as day length increases. LH and FSH act on the gonads in a successive and synergistic manner, initiating sexual maturation and maintaining cyclic reproductive function (Silvia et al., 1987).

Luteinizing hormone (LH) and follicle stimulating hormone (FSH) are members of the glycoprotein hormone family. They are heterodimers comprised of a common α-subunit (αGSU) and distinct β-subunits that confer biological specificity (LHβ and FSHβ). Until now it was thought that regulation of gonadotropin secretion occurs on the mRNA synthesis level of their subunits. However, not in all animals a close correlation exists between the concentration of gonadotropic hormones in the total circulation of their content in the pituitary and the level of corresponding subunits (LHβ, FSHβ and α) mRNA.

Expression of FSHβ and α-subunit genes

FSH synthesis and secretion is regulated by protein and steroidal factors on all levels of the hypothalamus-pituitary-gonadal axis. Recent investigations of transcriptional regulation of the FSHβ-subunit gene expression in different species reveal both conserved and species-specific regulatory mechanisms are involved.

Siberian hamsters exhibit seasonal variation in FSH levels. These changes can be recapitulated in laboratory animal by altering daily light exposure. In their study on Siberian hamster Bernard et al. (2000) found a high correlation between the patterns of change in serum FSH and pituitary FSHβ mRNA levels. After photostimulation the increase in serum FSH concentration and levels of both pituitary FSHβ and α-subunits were significantly elevated. However, the increase in α mRNA levels in the pituitary following photostimulation was modest compared to the increase in FSHβ mRNA (Bernard et al., 2000).

The existence of a correlation between the level of FSHβ mRNA and its translation product in hamster may indicate that the regulation of FSH synthesis in these animals takes place at the stage of transcription. The authors (Bernard et al., 2000) point out that a lower level of α-subunit synthesis after photostimulation may be due to its sufficient abundance relative to the β-subunits. The occurrence of large amounts of α-subunits is necessary because it can dimer with both FSHβ and LHβ-subunits as well as with thyroid stimulating hormone β (TSHβ). The increase in α-subunit mRNA accumulation could also be related to seasonal variations in the production of TSH, as in hamsters during the long days the α-subunit mRNA increases the synthesis of the hormone. In pars tuberalis mRNA levels of α and TSHβ are much higher during the long than short days (Bockmann et al., 1996).

In the horse, mean plasma concentration of FSH and pituitary content of FSH are relatively constant throughout the year (Alexander and Irvine, 1986). However, mean FSH concentration and pulse amplitude are high during the middle of the anovulatory season and declining during the last 60 days of this season (Freedman et al., 1979). Townsend et al. (2009) found that in the nonbreeding season pituitary content of FSHβ mRNA was unambiguously increased. In addition, during the breeding season, the pituitary content of α mRNA was increased in comparison to the non-breeding season (Townsend et al., 2009).

This inverse relationship between α mRNA and FSHβ mRNA levels may be the result of a decrease in GnRH concentration during the seasonal anestrus in the hypothalamus and lower GnRH pulse frequency (Kaiser et al., 1997; Hart et al., 1984). The parameters of the GnRH signal pattern initiate and maintain specific gonadotrope responses, with alterations in pulse amplitude or frequency resulting in selective gene expression. *In vitro* studies with superfused primary rat anterior pituitary cell have shown that varying GnRH pulse frequencies differentially affect the magnitude of stimulatory response of the gonadotropin subunit mRNA levels. FSHβ mRNA levels were stimulated to the greatest extent by a lower GnRH pulse frequency (every 2 h) than α and LHβ mRNA (every 30 min) (Kaiser et al., 1997). These *in vitro* data are consistent with observations *in vivo* (Dalkin et al., 1989). In seasonal reduction hypothalamic GnRH content and release contribute to a prolonged phase of melatonin secretion. Grubaugh et al. (1982) suggest a clear pineal involvement in seasonal reproduction patterns. In mares pinealectomy blocked the ability to respond to photostimulation (Grubaugh et al., 1982).

Although changes in GnRH pulse frequency may explain some differential regulation of FSH and LH secretion, many other factors are involved in this mechanism. Estrogens generally have a suppressive effect on FSHβ mRNA expression at the pituitary level. The mechanisms mediating this effect are not yet known. In the mare, mean circulating estradiol concentration remains low during the anovulatory season and increases during the last stages of the transitional period (Freedman et al., 1979).

In vivo studies in rats showed the suppressive action of inhibin on FSH release. Also during the estrous cycle of mares mean peripheral concentration of inhibin and FSH is inversely related (Bergfelt et al., 1991). In addition, inhibin concentration is lowest during winter and highest during summer. Inhibin probably produces its effects on FSH by antagonizing activin which stimulates intracellular signalling leading to enhanced expression of the FSHβ-subunit and FSH secretion. The changes in inhibin and estradiol concentration in the annual reproductive cycle, could be another factor responsible for differences in the level of expression of FSHβ-mRNA. The reason for the decline of α-subunit mRNA during non-breeding season in mares may be, at least partially, reduced secretion of LH and FSH. In addition, activin is known to decrease common α gene transcription (*Cga*) (Attardi et al., 1995).

Expression of LHβ-subunit gene

Townsend et al. (2009) found no relationship between the rate of LH synthesis and release in horses. During anoestrus the LH levels in both peripheral blood and the pituitary gland were significantly reduced (Hart et al., 1984), while the LHβ-subunit mRNA did not change seasonally (Townsend et al., 2009). Similarly in sheep, with obvious seasonal changes in frequency and amplitude of LH pulses, there is no detectable change in the LHβ-subunit mRNA level (Brooks et al., 1993). In the Siberian hamster LHβ mRNA levels and its translation product (LH) did not change significantly following photostimulation (Bernard et al., 2000).

In ewes in the luteal phase of estrous cycle, LH level in plasma is significantly higher than during anestrus. It is suggested that increased secretion of LH in the luteal phase is inter alia due to increased release of GnRH from the hypothalamus and GnRH-R expression in the anterior pituitary. Higher frequency of GnRH pulses in the luteal phase of sheep is probably responsible for the elevated LH secretion in these animals (Ciechanowska et al., 2008). In the pituitary estradiol modulates GnRH-mediated release of LH. Its effect is largely dependent on the physiological status of the animal; estradiol has a positive effect on the regulation of LH release during the breeding season but not during seasonal anestrus (Moss and Nett, 1980). Emphasis is given here to the role of melatonin, the pineal hormone that provides information about the changing day length in the regulation of gonadotropin secretion. Studies in which ewes during anestrus were treated with melatonin (in physiological quantities typical of winter) have shown that its high level in the body and prolonged exposure to its effects, led to activation of hypothalamic-pituitary axis GnRH / LH, after which they entered a phase of estrus (Arendt et al., 1983). Melatonin can regulate gonadotropin and prolactin secretion. Acting in the ventromedial region of the mediobasal hypothalamus melatonin, possibly through dopaminergic neurons, it regulates GnRH-induced LH secretion. In pars tuberalis, independently of the hypothalamus, melatonin regulates prolactin secretion (Lincoln et al., 1997).

Cytological configuration of the equine hypophysis may provide the morphological basis for the intrahypophysial control of fertility. Probably the main mechanism underlying the differential release of LH and FSH throughout the annual reproductive cycle of the mare is seasonal pattern in the density of gonadotrophs of the pars tuberalis. In sexually active females a larger proportion of monohormonal gonadotrophs (luteinizing hormone monohormonal and follicle-stimulating hormone monohormonal gonadotrophs) was observed (Tortonese et al., 2001).

***GnRH* gene expression**

GnRH represent the primary neuroendocrine link between the brain and the reproductive system. Therefore it seems that changes in GnRH mRNA expression should be a key mechanism controlling the onset of the breeding season and reactivation of the reproductive axis in seasonal anestrus. In the Syrian hamster, no influence of photoperiod on *GnRH* expression was detected. After a 16-week exposure of hamsters to short photoperiod, their GnRH mRNA levels were no different from the control group of animals maintained in long photoperiods, despite the existence of functional differences of testes reflected at the endocrine level in a marked difference in serum testosterone concentration. Also no significant difference in GnRH cell number in the hamster forebrain was found after exposure to different photoperiods (Brown et al., 2001). It is unlikely that changes in the degree of GnRH mRNA expression had a major impact on the neuroendocrine mechanism responsible for modulation of the activity of the reproductive axis of hamsters.

There is no clear relationship between GnRH mRNA levels and actual transcriptional activity in the ewes. The study on ovariectomized, progesterone-estradiol treated ewes have shown the lack of close relation between transcriptional activity of *GnRH* gene and GnRH/LH release (Kirkpatrick et al., 1998). In addition, progesterone acting in the hypothalamus exerted a suppressive influence on GnRH release but not on the *GnRH* gene expression (Ciechanowska et al., 2008).

Expression of *GnRH* receptor gene

In the mare no seasonal changes in GnRH receptor in the anterior pituitary were observed (Hart et al., 1984). Also, there are no significant seasonal changes in GnRHR mRNA levels (Townsend et al., 2009). However, in anestrous sheep, the level of GnRHR mRNA in the anterior pituitary and in the hypothalamus is significantly lower than in the luteal phase of the estral cycle (Ciechanowska et al., 2008).

The physiological relevance of the gene expression of GnRH-R in the hypothalamus and its role in regulation of GnRH secretion remains unclear.

In sheep the GnRH-R gene expression in the anterior pituitary is closely related to the estrogen and progesterone concentrations and GnRH pulse frequency (Kirkpatrick et al., 1998). It appears that the GnRH and estradiol, in the absence of progesterone, interact to upregulate GnRH-R expression in preparation for the preovulatory LH surge (Kirkpatrick et al., 1998). Probably a low level of GnRH-R mRNA in the pituitary during anestrus is due to reduction in secretion of estradiol and GnRH pulse frequency. In turn, increased expression of GnRH-R gene in the pituitary of sheep in the luteal phase may be the result of stimulating effect of elevated concentrations of estradiol in the circulation, an increase of GnRH pulse frequency and the lack of suppressive action of progesterone. However, the mechanism of the inhibitory effect of progesterone on the GnRH-R gene expression in the anterior pituitary is not understood well yet.

Effect of carbon monoxide (CO) on the regulation of gonadotropin synthesis

In the body, carbon monoxide (CO), in addition to nitric oxide (NO), is one of the main gaseous carriers of information, and thus has an impact on many physiological processes. Its best known role is as a mediator in the cardiovascular system, where it causes relaxation of vascular muscle, leading to an increase in blood flow (Zhang et al., 2001). Molecules of this gas are formed in the body from the degradation of heme by the heme oxygenase (HO). The action of HO results in equimolar amounts of CO, biliverdine and iron ions Fe^{2+} being formed (Tenhunen et al., 1969). Three heme oxygenase isoforms have been identified: inducible HO-1, the presence of which is mainly confined to the spleen and liver; HO-2, the constitutive form with a wide expression in the body including the brain; and HO-3, the isoform with low catalytic activity of heme, whose function is not fully understood (Maines, 1992).

The presence of heme oxygenase-2 in brain structures involved in hormone secretion, in the preoptic area, in the mediobasal hypothalamus (Brann et al., 1997) and in the pituitary (Aleandreanu and Lawson, 2002) and the high CO production rate in hypothalamus (Laitinen and Juvonen, 1995) support the role of CO in neuroendocrine regulation and other physiological functions (Maines, 1993; Aleandreanu and Lawson, 2002). A study on ovariectomized female rats has demonstrated that hormone release from anterior pituitary appears to be influenced by agents that would alter endogenous levels of CO (Aleandreanu and Lawson, 2002). These results suggest that CO may be a positive modulator of LH and prolactin secretion. However, in the case of FSH such a relationship was not observed. Infusion of heme, a substrate of heme oxygenase into the medial preoptic area and median eminence-arcuate nucleus complex, where the GnRH neurons are located did not change the profile of gonadotropin secretion (Aleandreanu and Lawson, 2002).

Heme oxygenase HO-2 is predominantly present in the retina (Nishimura et al., 1996). A study in the golden hamster showed that the activity of this enzyme, measured by the level of bilirubin was significantly higher at midday than at midnight. A higher degree of conversion of heme into bilirubin, after one hour of light stimulation during the night, and a decrease in heme oxygenase activity after the similar one hour of darkness during the day indicates that the dominant factor in the regulation of this activity is stimulation of the eye retina by light (Sacca et al., 2003).

It is suggested that part of the intracellular pathway is activated by a signal of light, which may explain the changes in heme oxygenase activity is dopamine. It has been shown in several animal species that the light in the retina stimulates the synthesis, release and metabolism of the neurotransmitter (Godley and Wurtman, 1988) and that dopamine inhibits N-acetyl-transferase (Jaliffa et al., 2000), a crucial enzyme in the biosynthesis of melatonin. In the golden hamster heme oxygenase activity in the retina was stimulated by exogenous dopamine, both during the day and night (Sacca et al., 2003).

In 1996, Dan A. Oren presented a model of humoral phototransduction which assumes that the two endogenous gases, carbon monoxide (CO) and nitric oxide (NO) are the signals of day for the nervous system. His hypothesis is based on several assumptions:

1. exposure to light increases the activity of nitric oxide synthase (NOS) and heme oxygenase. Consequently it increases the amount of CO and NO;

2. light has the ability to dissociate CO and NO from the heme;

3. changes in the amount of bonds decomposing CO-Hb are seasonal and diurnal;

4. hemoglobin is not only a scavenger of NO and CO, but also their transporter.

According to Oren, these two gases are formed under the light influence in retina's vessels and with hemoglobin participation, without the systemic circulation, reach the perihypophyseal vascular complex and thence the brain and pituitary, where they can exert an influence on the regulation of the pineal gland and the corresponding nerve centres (Oren, 1996).

In several animal species, a possibility has been shown for infiltration of neurohormones, steroid hormones and pheromones from the cavernous sinus venous blood, in which venous blood outflows from the eye, to arterial blood supplying the brain and the pituitary (Krzymowski et al., 2001). Thus, if such a large molecule that exceeds 1000 daltons in size can penetrate this area, this is even more possible for small gas molecules (Krzymowski and Stefańczyk-Krzymowska, 2008).

Changes in release of GnRH pulse pattern do not explain the preferential stimulation of the synthesis and secretion of gonadotropins in the annual reproductive cycle. It seems that occurrence of the seasonal modulation of reproduction in seasonal breeding animals is due to changes in the activity of several neuro-endocrine systems in relation to GnRH release.

The effect of carbon monoxide on regulation of the hypothalamic-pituitary-gonadal axis has not been studied to date. There is substantial evidence to suggest that it may play a role in the transduction of information on day length. The study of this mechanism, and the potential effect of CO on the seasonally changing expression of reproduction-related genes and proteins, could bring insights into the understanding of periodic reproduction and infertility.

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Ekspresja genów podjednostek gonadotropin, GNRH i receptura GnRH oraz rola tlenku węgla u zwierząt rozmnażających się sezonowo

STRESZCZENIE

Sezonowość w rozrodzie występuje głównie u gatunków dzikich i jest wynikiem naturalnej selekcji. Sygnały do rozpoczęcia czy też zakończenia okresu aktywności rozrodczej, zarówno środowiskowe, jak i hormonalne, ostatecznie skupiają się na neuroendokrynnym szlaku – kontroli syntezy i sekrecji przysadkowych hormonów, luteinizującego (LH) i folikulotropowego (FSH), przez neurony GnRH-egriczne podwzgórza. Zmienna częstotliwość pulsów GnRH jest nie tylko głównym elementem regulującym podstawowe i okołoowulacyjne uwalnianie gonadotropin, ale może też pełnić rolę w specyficznej aktywności transkrypcyjnej genów ich podjednostek. Zmiana pulsacyjnego wzoru uwalniania gonadoliberyny nie tłumaczy jednak w pełni preferencyjnej stymulacji syntezy i sekrecji poszczególnych gonadotropin w rocznym cyklu reprodukcyjnym. W regulacji tej będzie miał również udział mechanizm niezależny od GnRH. Wydaje się, że głównym czynnikiem odpowiedzialnym za występowanie sezonowej modulacji reprodukcji u owiec i innych ssaków są znaczne zmiany w odpowiedzi systemu GnRH na sterydy gonadowe. Wpływ tlenku węgla na regulację osi podwzgórzowo-przysadkowo-gonadalnej nie jest do tej pory zbadany. Istnieje jednak wiele przesłanek świadczących o tym, że może on pełnić funkcję w przekazie informacji o długości dnia świetlnego. Obecność oksygenazy hemowej-2 w obszarach podwzgórza istotnych w regulacji funkcji sekrecyjnej przysadki oraz w samej przysadce sugeruje, że CO, produkt działania tego enzymu, może uczestniczyć w regulacji sekrecji hormonów przez ten gruczoł.