



## **THE ROLE OF MELATONIN AND BROMOCRIPTINE IN THE REGULATION OF PROLACTIN SECRETION IN ANIMALS – A REVIEW\***

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### **Abstract**

Changes in the concentration of melatonin and prolactin are associated with response to day length. The factors that stimulate the release of PRL include, among others, TRH, VIP, endorphins, oestrogen, and adrenaline. PRL secretion inhibitors include DA, GABA, progesterone and bromocriptine (exogenous compound), used in the treatment of hyperprolactinemia  $D_2$  receptor agonist. The biological activity of this compound is to stimulate dopamine  $D_2$  receptors in the pituitary, which inhibits PRL secretion via the tuberoinfundibular pathway (Fitzgerald and Dinan, 2008). In sheep treated with bromocriptine there is a decrease in PRL concentration and an increase in the sensitivity of cells producing LH to GnRH, but there is no disturbance in the course of the estrous cycle. Rams show decreased libido and changes in sexual behaviour. The administration of bromocriptine throughout the period of sexual activity and the period of rearing offspring affects maternal instinct, which involves the inhibition of PRL secretion. It is not clarified whether the effect of bromocriptine on sexual behaviour is associated with its direct impact on behavioural centres in the brain, or indirectly through the regulation of PRL secretion. However, the seasonal variations in the effects of bromocriptine on sexual behaviour can strengthen the hypothesis that the effect of bromocriptine on sexual development behaviour is associated with changes in the intensity of PRL secretion rather than by the inhibition of behavioural bromocriptine brain centres. The process of regulation of prolactin secretion by bromocriptine requires further examination.

**Key words:** bromocriptine, prolactin, melatonin, seasonality

Many animals show a cyclic pattern of physiological processes depending on seasonal changes. These particularly concern the mating period, migration, aestivation and hibernation, which occur during seasons of the year characteristic of a given species. These phenomena require the animals to predict environmental changes and to metabolically prepare for them in advance. Such endogenous rhythms and cycles

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are known as circadian and infradian. It is now clear that circadian and infradian biological rhythms play a fundamental role in the animals' adaptation to external environmental conditions. Therefore, animals have the ability to synchronize their endogenous rhythms with changes in the surrounding environment (Hastings et al., 2007).

Breeding season of organisms of many species is strongly associated with the time of the year and environmental conditions. In order to ensure the brood has the greatest possible chances of survival, the adaptation mechanisms were developed, which aimed to integrate the endogenous reproductive cycle of the species with the changing factors of the exogenous environment. Key factors in regulating the reproductive cycle in seasonal animals are changes in the length of the day (Gómez-Brunet et al., 2008).

Changes in seasonal profile of prolactin during extension or shortening of a light phase influence behaviour and productivity of animals. Prolactin (PRL) is a hormone built from amino acids composing a single chain. It belongs to the group of somatomammotropins. It is one of the many hormones produced in the anterior lobe of the pituitary. The hormone was first detected in 1928 in the animals' pituitary cells and was isolated in 1932, whereas in 1971 the human prolactin was purified. Prolactin is characterised by heterogeneity in the construction of molecules. The difference is the amount of amino acids in the chain (197–199) and the molecular weight (23–24 kDa). It contains 199 amino acids and 3 internal sulphide bridges in humans. As a result of differences in the molecular weight of prolactin, the hormone is divided into isoforms occurring in the blood in different quantities. In the human blood prolactin circulates mainly as a form of little (small) and its molecular weight is 23 kDa. There is a little less of a form of big (big) (48–56 kDa) and of polymer big – big (more than 100 kDa). In the blood of dogs, in addition to form big – big and big, native forms and fragmented forms were detected. Prolactin has similar metabolic activity, chemical structure and active centre to GH, however its homology with the growth hormone is only 16%. The ability to bind zinc affects the durability of mammotropin molecule. Prolactin secretion occurs in eosinophil lactotrope cells of the pituitary gland. The presence of prolactin and receptors of the hormone were also detected in posterior pituitary (neurohypophysis) (Gregory et al., 2007), as well as in structures of the limbic system such as amygdala, hypothalamus and hippocampus (Bartke et al., 1987). The existence of the prolactin receptors, besides the pituitary of the brain, was found in a mammary gland, liver, adrenal glands, kidneys and ovaries (Vonderhaar et al., 1985). These receptors are composed of two subunits  $\alpha$  and  $\beta$  and show significant affinity to other lactogenic hormones, among others placental lactogen and the growth hormone. Prolactin acts via a specific prolactin receptor (PRL-R), which belongs to the superfamily of class 1 cytokine receptors (Bole-Feysot et al., 1998; Freeman et al., 2000). It is found in the cell membrane and consists of a single hydrophobic transmembrane domain which divides the receptor into an extracellular ligand binding domain and an intracellular domain, responsible for intracellular signal transduction (De Bellis et al., 2008). Depending on the length of the intracellular domain, three isoforms of the PRL-R were identified in humans: short (288aa), intermediate (376aa) and long (598aa) (Bole-Feysot et al., 1998). In

humans only the long isoform of the receptor is highly active in signal transduction (Bole-Feysot et al., 1998; Wylot et al., 2003). After prolactin binds to PRL-R, the receptor is dimerized and activated, which initiates a cascade of events involving the JAK2/STAT pathway, which is the main signalling pathway. In the first place, phosphorylation of the receptor's intracellular domains activates Janus-activated kinase 2 (JAK2), which triggers tyrosine phosphorylation of the long isoform, which is the binding site of STAT (signal transducer and activator of transcription) proteins. They are secondary signal transducers and transcription activators – mainly STAT5a and STAT5b, and to a lesser extent STAT3 and STAT1. Phosphorylated STAT dissociates from the receptor, forms a homo- or heterodimer and translocates to the nucleus, activating specific sequences in the gene promoter regions to stimulate their transcription. One of such gene stimulating products is interferon regulatory factor-1 as well as suppressor of cytokine signalling (SOCS), which play an important role in the prolactin mechanism resulting from activation of PRL-R (De Bellis et al., 2008; Freeman et al., 2000). The JAK2/STAT signalling pathway is activated simultaneously with the independent Ras/Raf/MAP kinase pathway, where MAP (mitogen-activated protein) is activated. Phosphorylated tyrosines in the intracellular PRL-R domain become the attachment site for Shc/Grb2/SOS adaptor proteins, which link the receptor to the Ras/Raf/MAP kinase cascade. The activation of this cascade is essential for proper immune response (Freeman et al., 2000).

Prolactin is produced in cells in the central nervous system, the placenta and myometrium (Ben-Jonathan and Hnasko, 2001). The source of the synthesis of PRL may be some cancer cells (Brody and Kruger, 2006). The number of lactotrope cells is always higher in females than in males, during pregnancy the number and the size of the cells increases. The concentration of PRL in the organism of the female exceeds the content of this hormone in males, which is associated with the stimulant action of estrogens (Ben-Jonathan and Hnasko, 2001). Without prolactin the maintenance of corpus luteum function is not possible in the case of pigs or certain species of rodents (Harris et al., 2004). The effect of the prolactin on the organism of mammals is most apparent through changes in mammary gland area. It is essential for its development and subsequently to initiate and maintain lactation. The influence of this hormone on more than 300 processes is proved, which would not be possible without the participation of PRL. Prolactin plays the role in the functioning of the immune system, the regulation of the sexual behaviour, the occurrence of the phenomenon of maternal instinct. In addition it participates in the process of angiogenesis, the support of the water-electrolyte equilibrium of the organism and in phenomena of steroidogenesis and folliculogenesis (Goffin et al., 2002).

### **Regulation of prolactin secretion**

Regulation of the secretion of prolactin by the lactotroph pituitary cells is complex, and the most important role in this process is played by hypothalamus (Freeman et al., 2000; Grattan, 2001). Other sites of prolactin synthesis are the telencephalon, cerebral cortex, amygdala, brainstem and cerebellum. PRL detected in the hypothalamus was found to be locally produced. Removal of the pituitary gland has no effect on the presence of prolactin in the male rat hypothalamus, and decreases the

amount of this hormone in female rats. Among the factors that modulate PRL secretion and synthesis in the hypothalamus are ovarian steroid hormones. About 30% of medial hypothalamic neurons have oestrogen receptors, as evidenced by a decrease in the amount of hypothalamic prolactin in ovariectomized animals. The modulation of hypothalamic synthesis and release of prolactin is not completely understood and requires further research (Freeman et al., 2000). Factors inhibiting the secretion of prolactin are dopamine (DA), GABA acid (gamma-aminobutyric acid) and progesterone (McCann et al., 1984; Mizuina et al., 1985). However, the most important inhibitor of prolactin is dopamine, and its inhibitory action is done by  $D_2$  receptors present in the lactotrope pituitary cells (Ben-Jonathan, 1985; Arbogast and Voogt, 1996). Hypothalamic dopamine is secreted from dopaminergic neurons located ventrally in the arcuate and periventricular nucleus. They form three pathways that guide axons to the median eminence (TIDA – hypothalamic tuberoinfundibular dopamine neurons), to the neural and intermediate lobe (THDA – tuberhypophyseal neuroendocrine dopaminergic neurons) and exclusively to the neural lobe (PHDA – periventricular hypophyseal dopaminergic neurons) (Goudreau et al., 1985). Released from the eminence through the long loops of portal vessels and from the short loops of the neural and intermediate lobe, dopamine may reach the anterior pituitary and lactotrophs. Dopamine, while binding with  $DA-D_2$  receptors on the surface of lactotrophs, inhibits the secretory activity of these cells. Through  $D_2$  receptors it inhibits PRL secretion and causes inhibition of adenylate cyclase by  $G_i$  protein with closure of the calcium channel by  $G_o$  proteins. Together with cell membrane hyperpolarization and calcium channel closure induced by dopamine stimulation of the potassium channels, this leads, via  $G_{13}$  protein, to a decrease in the cell calcium levels and thus inhibits PRL secretion (Lincoln and Clarke, 2002).

Through  $G_i$  protein dopamine counteracts the activation of VIP receptors, the end result of which is increased concentration of calcium ions in prolactin cells. Via  $G_{13}$  protein it also blocks the influx of calcium ions caused by the generation of second messengers – diacylglycerol (DAG) and inositol triphosphate ( $IP_3$ ) – as a result of stimulating TRH or neurotensin (NT) receptor. Inositol triphosphate ( $IP_3$ ) opens calcium channels in the endoplasmic reticulum, which causes a transient increase of  $[Ca^{++}]$  in prolactin cells and releases the hormone. Through activation of protein kinase C, diacylglycerol may inhibit the opening of potassium channels and membrane depolarization, which indirectly stimulates the influx of calcium ions. This inhibits PRL release after a short-term increase in its concentration (Ben-Jonathan and Hnasko, 2001). This mechanism is probably responsible for pulsatile secretion of PRL. A similar inhibitory effect is shown by noradrenaline, but the inhibiting effect of DA is much stronger (Lincoln and Clarke, 2002). Through  $D_2$  receptor dopamine inhibits PRL secretion whereas activation of  $D_1$  receptors stimulates prolactin secretion. It was shown that  $D_1$  receptor agonists stimulate PRL secretion in sheep, while low DA concentration increases prolactin secretion from rat pituitary cells (Ben-Jonathan and Hnasko, 2001). By diffusion through the choroids plexus, prolactin penetrates into cerebrospinal fluid and impacts the central nervous system. By retrograde blood flow from the anterior pituitary to the hypothalamus, prolactin reaches the brain (Mezey and Palkovitz, 1982). However, the increase in the concen-

tration of PRL acts in the hypothalamus, stimulating the synthesis and release of DA to the pituitary portal system (Poletini et al., 2010). Studies on rats showed that the feedback between PRL and DA in the final period of pregnancy and then in lactation does not play a significant role in regulating the secretion of the PRL (Ben-Jonatan and Hnasko, 2001; Grattan, 2001).

The factors stimulating the release of prolactin are: thyroid-stimulating hormone (TRH), vasoactive intestinal peptide (VIP), epinephrine,  $\beta$ -endorphins and oestrogens (Frawley and Neill, 1981; Leong et al., 1983). Recently the different types of lactotrope cells in the anterior lobe of the pituitary have been noted. The process of cell differentiation for each type is not completely known and seems to have a relationship with the various stages of their maturity. However, depending on which of the 3 types of lactotrope PRL is produced in, the hormone can serve different functions. In the last few years a big group of peptides stimulating the release of PRL has been noted. They were identified in different animal species including mammals. These compounds (PrRPs – prolactin releasing peptides) vary in terms of the amount of amino acids from which they are constructed and have different effects on PRL secretion, depending on which type of lactotrophs they affect (Tachibana et al., 2011). So, for example, PrRPs-31 stimulates the secretion of the PRL from lactotrophs type II and type III, but does not show such an effect on type I. It has been proven that this peptide induces the release of PRL to a lesser extent than it does in the case of TRH and VIP (Christian et al., 2007). Through experimentation it was found that in GH3 cell line, GH and PRL were produced. The presence of receptors for TRH, VIP and of epithelial growth factors was found in this cell, but there was no evidence of DA receptors. PRL made in specific cells of the MMQ (a unique prolactin-secreting rat pituitary cell line) exercised influence on the expression of DA  $D_2$  receptors, ETa (endothelin) and oxytocin. Prolactin from different cell types has a direct impact on tissues as a growth factor, neurotransmitter, or as immune modulators in auto or paracrine way (Stojilkovic et al., 2010).

### **Day length and prolactin secretion**

Photoperiod has a significant influence on seasonal and daily changes of PRL concentration as its length initiates changes of melatonin concentration (Morgan, 2000). An oscillator located in SCN (suprachiasmatic nucleus of the hypothalamus) controls daily changes in PRL concentration. The pineal is also responsible for these changes because there is no increase of PRL secretion at the end of the day in animals deprived of the pineal. In addition, daily release of prolactin is influenced by dopaminergic system. Attenuation of the activity of this system is a prerequisite for generating an increase of PRL concentration under the influence of melatonin (Miszta et al., 1997, 2001). The main neurosensory receptor of the circadian system is the eye retina; it receives light stimuli that are transmitted along the optic nerves to suprachiasmatic nucleus (SCN). Activity of the SCN oscillator is stimulated by retinal cone and rod cells. Research has shown the presence of a photosensitive pigment (melanopsin) in retinal ganglion neurons, which is responsible for regulating biological rhythms, located in the axons of the retinal hypothalamic pathway that connects retina with SCN. In response to a light stimulus, retinal cells induce an

impulse by secreting the neurotransmitters: glutamic acid and the pituitary adenylate cyclase-activating polypeptide (PACAP) of the retinal hypothalamic pathway to SCN (Hannibal, 2002). The secretory activity of SCN neurons is increased in the light phase, and during the dark phase this activity weakens under the influence of melatonin (Molik et al., 2009). SCN and PT (pars tuberalis) is where biological clock genes (*Bmal1*, *Clock*, *Per1*, *Per2*, *Cry1*, *Cry2* and *CK1 $\epsilon$* ) are located (Lincoln and Clarke, 2002). Rhythmic change in the expression of these genes occurs depending on the light signal. *Per1* gene is expressed at dawn and *Cry* at dusk, with an increase in melatonin concentration (Lincoln, 2006). *Per1* expression is melatonin dependent because pinealectomy blocks the PT *Per1* rhythm, without having any impact on expression in the SCN, and repeated injections of melatonin in pinealectomized animals can reinstate the cyclical *Per1* transcription in the PT (Lincoln and Clarke, 2002).

In mammals, information about seasonal changes in day and night length is received based on the generated melatonin signal. Experiments with sheep demonstrated that expression of biological clock genes (*Cry1*, *Per1*, *RevErb $\alpha$* ) is strongly associated with melatonin secretion. Activation of the *Cry1* gene occurs in response to increased melatonin secretion, whereas expression of the *Per1* gene takes place at dawn and is associated with a decrease in melatonin secretion (Hazelering et al., 2004). A study with Japanese quail exposed to long photoperiod showed that *TSH $\beta$*  (thyrotropin beta subunit) and *Eya3* (cofactor eye absent 3) are the first genes to become activated in the PT already during the first day of exposure to long day conditions. In seasonal mammals, PT plays a direct role in regulating the annual PRL cycle, with *Eya3* protein serving as a transcription cofactor and enzyme. *Eya3* protein is the strongest gene activated in response to the long day in sheep, and is responsible for generating a photoperiodic molecular response in mammals and birds (Dupre et al., 2010).

Melatonin receptors are widely distributed in the central nervous system, mainly in the SCN, PT, retina, cerebral cortex, and hippocampus. An especially strong binding of 2-<sup>125</sup>I-iodomelatonin was obtained in suprachiasmatic nuclei, the thalamus and the pars tuberalis (Lincoln et al., 2003). The PT consists of specific secretory cells, FS cells and cells characteristic of the anterior pituitary. Pars tuberalis cells show high variation, both morphological and in secretory activity during the annual cycle. In all the animals that have been investigated to date, both seasonal and aseasonal, large numbers of melatonin receptors were found in PT cell membranes. In rats their density changes during the day and is not light dependent. This suggests that these cells contribute to the transduction of melatonin information to the endocrine system (Lincoln et al., 2003). A study with rams showed that the melatonin rhythm in HPD (hypothalamo-pituitary disconnected) animals remains unchanged but the circadian prolactin rhythm disappears (Lincoln and Clarke, 1994). Two different mechanisms modulate the action of melatonin on prolactin secretion. In the case of circadian rhythm, melatonin stimulates prolactin release directly or via tuberallin (two tuberallin proteins, I and II, with different molecular weights were detected in bovine PT cells). However, the effect is short and only concerns the prolactin stored in the pituitary lactotroph cells (Misztal et al., 1999). This may



suggest that tuberalin activates the prolactin gene expression in lactotroph cells (Johnston, 2004).

It is not completely clear how the PT regulates the seasonal rhythm of PRL. There is evidence to show that in several species of rodents TSH is produced by the PT and, according to the latest research, it can play a key role in bird photoperiodic processes. In sheep, over 90% of PT cells are chromophobe cells that produce tuberalin. The identification of tuberalin has not been clarified until today, but it is subject to certain criteria that seem to be met by SP (substance P). Injection of SP directly into the pituitary portal system was shown to stimulate PRL release in rats, but this effect does not occur after intravenous injection (Wood and Loudon, 2014). The role of tachykinins in regulating seasonal hormonal rhythms is not well understood and requires further research (Skinner et al., 2009).

A long MEL signal, typical of short day, inhibits PRL secretion in the pituitary gland. Research has shown that long-term administration of MEL to both rams and ewes (e.g. using subcutaneous melatonin implants) during the long day inhibited PRL secretion (Ciechanowska et al., 2013). The long melatonin signal from the short photoperiod or a constant signal emitted by the melatonin implant may inhibit PRL secretion by reducing the release of tuberalin from the pars tuberalis (Morgan, 2000).

Melatonin administered to the third ventricle of the brain stimulates PRL secretion, whereas MEL infused directly into the anterior pituitary has no effect on changing plasma prolactin concentration in rats (Kamberi et al., 1971). Melatonin has no impact on PRL secretion in castrated rats but it stimulates PRL secretion in uncastrated animals (Vaughan et al., 1979).

The secretion of PRL drops as the day shortens, which was observed in sheep. High concentration of melatonin sustained in such conditions results, on the one hand, in the decrease of the secretion of prolactin, on the other it sends the organism into reproductive activity (Misztal et al., 1999). The research revealed that extending the light phase in short-day conditions does not result in the increase of PRL concentration in the blood. The simulation of the long day caused a short-lived increase of the concentration of this hormone, however later it returned to the endogenous rhythm. PRL secretion depends on the melatonin signal sustained under the influence of changes in the length of day. In seasonal animals the importance of biological clock genes remains a significant factor of endogenous rhythms (Sweeney et al., 1999).

The increase in secretion of prolactin in the conditions of a long day is accompanied by high activity of hypothalamic dopaminergic system (Thiery, 1991). Dopamine is the main inhibitor of prolactin secretion and dopaminergic neurons of mediobasal hypothalamus play an important role in the control of prolactin secretion. The interaction of dopamine is conducted via at least two classes of dopamine  $D_1$  and  $D_2$  receptors, located on lactotrophs pituitary cells (Ben-Jonathan et al., 1989). Thus, a change in day length (melatonin profile), can modulate seasonal rhythm of prolactin. In contrast, prolactin influences the dopaminergic system activity by positive feedback (Lincoln and Clarke, 1995). In the short-day or by the action of exogenous melatonin, there was observed a decline in dopaminergic system activity and a decrease in the concentration of prolactin (Molik et al., 2013).

### **Bromocriptine and prolactin secretion**

Bromocriptine is a semi-synthetic derivative of ergocryptine impelling dopaminergic receptors ( $D_2$ ) in the pituitary. It is a substance demonstrating a wide range of effects on the organism of the animals. It inhibits the production and secretion of prolactin from the anterior lobe of the pituitary gland. In acromegaly it reduces the secretion of the growth hormone (Arihara et al., 2014). It inhibits the growth of pituitary adenoma (prolactinoma). In hyperprolactinemia it lowers the concentration of prolactin (Moloth, 2015). It shows antidepressant action. In parkinsonism it works on dopaminergic receptors in the substantia nigra, in the striatum, and in the limbic system, reducing the tremor and acinesia. It is well absorbed from the gastrointestinal tract. In 96% it is bound with plasma proteins (Li et al., 2013). It is completely excreted with bile and faeces (partly in the form of metabolites), in a small percentage of urine (Boyd, 1995; Besognet et al., 1995; Eftekhari and Mohammadalizadeh, 2009). Studies show that stimulation of dopaminergic receptors in the hypothalamo-pituitary area indicates a significant role of dopamine in regulating the release of sheep PRL (Dominguez-Gonzales and Genaro, 1994). Bromocriptine applied to sheep results in decrease of prolactin intensity and does not affect the functioning of the ovaries (Fuentes, 1986; Fuentes et al., 2006). In ewes, which were applied bromocriptine, the concentration of PRL in blood plasma reached a value of less than 1.5 ng/ml and such concentration may be sufficient to inhibit the tuberoinfundibular neurons (Andrews et al., 2002). Administration of bromocriptine in sheep does not affect the process of ovulation and rutting behaviour, however, it influences behaviour of females (Fuentes et al., 2006). Appropriately released prolactin significantly influences the maternal instinct and creates good relations with their offspring. Mother's organism exposed to its activity shows easy to notice instinctive behaviour. In the preparatory phase a ewe becomes calmer, in the final stage before delivery separates from the flock. It tries to provide the maximum comfort to itself and the best chance for a brood (Rushem et al., 2001). Such behaviour is caused by the endocrine system and particularly in regulation of the prolactin secretion. The conducted research proved that before birth, the significant increase of prolactin secretion occurs and after the birth the PRL concentration decreases. Application of bromocriptine as the prolactin blocker weakens the maternal instinct, leads to unusual behaviour, sometimes even aggression directed to their own offspring (Molik and Pieronkiewicz, 2011). In the case of sows, maternal instinct is manifested by several perinatal proceedings (including the construction of a nest). In the sows, which during this period were given the prolactin blocker bromocriptine, fall of interest in bedding and less care in preparation in place of birth was observed. Furthermore, during the rearing of piglets, the decline in the concentration of PRL caused by the bromocriptine activity was found in the increased aggressiveness of mothers in relation to piglets. There was also an increase in the amount of crushes of younglings by mothers (Mattioli et al., 1986). Low prolactin levels contribute to the shortage of milk, and even disable feeding. Studies indicate that bromocriptine has a significant impact on the changes of the concentration of prolactin in animals of different species. Applying of the above mentioned alkaloid brings about reduction in the concentrations of GH and PRL in the blood, which gives positive effects in the treatment of



galactorrhea. Excessive prolactin synthesis hyperprolactinemia can cause infertility, lack of sex drive, blurred vision. An overactive pituitary gland could lead to premature puberty. Excessive secretion of prolactin is responsible for disorders in gonadotrophic hormone secretion. As a consequence, in males libido drops or disappears and causes depression, and in females disorders of ovulatory cycle appear (Lincoln and Davidson, 1997). Persistent for a long time, high concentration of PRL produces a similar effect in mice, rats and rabbits. By eliminating hyperprolactinemia, sexual behaviour in mice and rats returns back to normal (Doherty et al., 1981). Disorders in the secretion of the PRL in the case of hyperprolactinemia lead to changes in sexual behaviour. Bromocriptine causes a definite decrease of PRL concentration in animals, only in situations when the hormone intensity is high (Johnson and Becker, 1987). Statistics do not show significant changes in PRL concentration after applying bromocriptine to animals, in which the level of this hormone was low (Besognet et al., 1995). Administration of bromocriptine to rams resulted in a weakening of their sexual behaviour. Hypoprolactinemia induced by bromocriptine activity does not cause a complete loss of sexual activity (Regisford and Katz, 1993). Studies suggest that depending on the species there are differences between the prolactin profile and sexual behaviour. The high level of PRL is associated with increased sexual activity in hamsters, and administration of bromocriptine stimulates males of mice and rats with hyperprolactinemia to copulate (Bartke et al., 1987). In rams high level of PRL, as well as extremely low during administration of bromocriptine, is associated with a decrease in the frequency of presentation of sexual behaviour (Regisford and Katz, 1993). In sexually active rats, which were administered dopamine and bromocriptine simultaneously, the increase of the activity is proved. However, the administration of the antagonists of dopamine receptors resulted in a decline in libido on these animals (Pfaus and Philips, 1991). It is not fully explained whether the impact of bromocriptine on sexual behaviour is linked to its direct effect on behavioural centres in the brain, or its indirect effect by regulating of the PRL secretion. Nevertheless, seasonal differences in bromocriptine influence on sexual behaviour can strengthen the hypothesis that the bromocriptine effect on sexual behaviour is associated with changes in the intensity of PRL secretion and not with suppression by bromocriptine of cerebral behavioural centres (Gloria et al., 1994).

It is easy to notice that both melatonin and bromocriptine have a significant effect on the secretion of prolactin. Thanks to the many possibilities of action and interaction with the seasonal rhythm that governs the seasonal animals, melatonin and bromocriptine have an influence, through prolactin, on aspects of the functioning of the organism such as lactation, sexual behaviour, instinctive behaviour, reproductive cycle and certain disorders. Deeper understanding of the mechanisms of their actions can contribute to advances in medicine, improvement of production, as well as improving the quality of animal products. For this reason, it is necessary to conduct further research in this area.

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