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THE IMPACT OF THE MOTHER ON THE HYPOTHALAMIC-PITUITARY-ADRENAL, HYPOTHALAMIC-PITUITARY-GONADAL AND SOMATOTROPIC AXES ACTIVITY OF OFFSPRING DURING POSTNATAL ONTOGENY

Abstract

During the rearing period, most of the physiological processes of offspring are under maternal regulation, which overcomes the influence of external environmental factors. Maternal deprivation activates the hypothalamic-pituitary-adrenal (HPA) axis of young mammal which in turn causes the adaptation of the developing organism to the new circumstances. It is considered that too early interruption of the mother-offspring ties may activate the not fully developed HPA axis and change the functions of the other hormonal systems of growing mammals. This article reviews the changes in the activity of the somatotropic and gonadotropic axes in young rodents and sheep during the physiological condition known as a rearing period and after maternal separation which is thought to be a stressful event in animal ontogeny. Furthermore, the current review also focus on the changes of the HPA axis hormone secretion of offspring caused by maternal deprivation.

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Introduction

Ontogeny includes a series of morphological and physiological changes from conception to formation of the mature organism. In the early stages of mammalian ontogeny the dominating processes are the growth connected with increasing number of cells and differentiation involving the qualitative changes of individual types of cells. Close coordination of these processes determines the normal postnatal development of offspring and leads to puberty (Ojeda, Jameson 1977; Jansen 1982; Wańkowska, Polkowska 2006; Wańkowska et al. 2008a; Wańkowska et al. 2008b; Wańkowska et al. 2010a; Wańkowska et al. 2010b; Wańkowska 2012; Wańkowska et al. 2012).

Birth, weaning and puberty are pivotal events in the mammalian postnatal ontogeny. According to them, there are following stages of development: neonatal, infantile, juvenile and pubertal. Neonatal and infantile stages are parts of the rearing period. This schema pertain to species with relatively long ontogeny (Ebling 2005; Wańkowska et al. 2008a; Wańkowska et al. 2008b; Wańkowska et al. 2010a; Wańkowska et al. 2010b).

During the rearing period, most of the offspring's physiological processes are under maternal regulation. Creating the psychoemotional and physiological bonds the mother reduces the influence of external environmental factors on the development of the young mammal (Levine et al. 1993; Van Oers et al. 1999). Furthermore, suckling plays a key role in the regulation of postnatal ontogeny. Endogenous opioids are synthesized in the offspring's brain during suckling (Smotherman, Robinson 1992) and are responsible for the psychoemotional connection between the mother and her young (Agmo et al. 1997). Disturbances between mother-offspring relations were observed after using of the opioid receptor antagonist (Kalin et al. 1995). Colostrum and the mother's milk are not only the source of balanced nutrients but also of immunoglobulins responsible for the modulation of immunological response of developing offspring (Fitzsimmons et al. 1994).

The HPA axis is responsible for the adaptation of the organism to the stress condition. Compared with other hormonal axes the activity of the HPA axis is inhibited the most during the rearing period. In rats between 4 and 16 day of life (rearing period) the quiescence of the HPA axis function is observed and only strong stressors like maternal separation appears to activate the stress axis. This incomplete adrenal response during the postnatal period is named Stress Hyporesponsive Period (SHRP), and is connected with the HPA axis immaturity (Levine et al. 1991; Levine et al. 1993; Dent et al. 2000).

Weaning is a strong stimulus of the HPA axis and is believed to influence the main physiological processes involved in progress of postnatal ontogeny. Despite this, maternal deprivation might be perceived as a physiological aspect of offspring development (Kuhn et al. 1990; Levine et al. 1993; Iqbal et al. 2005; Wańkowska et al. 2006; Polkowska, Wańkowska 2010; Wańkowska, Polkowska 2010).

Farm animal breeders due to economic reasons strive for the earliest possible separation of young from their mothers. However, numerous findings indicate adverse effects of maternal separation on the activity of young animals hormonal axes involved in growth, development and puberty (Juarez et al. 1988; Kuhn et al. 1990; Pihoker et al. 1993; Liu et al. 1997; Schmidt et al. 2004; Wańkowska et al. 2006; Polkowska, Wańkowska 2010; Wańkowska, Polkowska 2010). The effect of the maternal deprivation depends on species, age and experiment design. This review will focus on changes in the somatotropic and HPG axes activity during postnatal ontogeny. The emphasis will be paid to description of the central mechanisms of the growth and reproduction after maternal separation.

Somatotropic axis secretory activity during growth

Somatostatin and growth hormone releasing hormone (GHRH) are pivotal neuropeptides in the somatotropic axis. Their antagonistic influence regulates the growth hormone (GH) secretion. Somatostatin is synthesized in the periventricular nucleus (PVN) and the arcuate nucleus (ARC) of the hypothalamus and inhibits the secretory activity of GH cells in the pituitary. Growth hormone releasing hormone released from the ARC stimulates the synthesis and release of GH in the pituitary cells. Circulating GH suppresses its own synthesis through reducing of the effectiveness of the GHRH secretion and the enhancement of the somatostatin secretion (Farhy et al. 2003). Growth hormone elicits its effects directly in the cartilage or mature adipocytes or trough IGF-I (insulin-like growth hormone I) and IGF-II (insulin-like growth hormone II) which are mostly produced in the liver. In general, GH stimulates protein synthesis, which is reflected by increased amino acid uptake and decreased protein oxidation levels. Moreover, GH increases lipolysis and glycogenolysis activity (Bak et al. 1991; Weltman et al. 1994).

Secretory activity of the somatotropic axis is strongly related to the progress of ontogeny. In rats the postnatal increase in the GH secretion is observed. When the maturation of the feedback mechanism in the somatotropic and hypothalamic-pituitary-gonadal (HPG) occurs the gradual fall in the GH release appears (Bermann et al. 1994). During puberty in rats high concentration of plasma GH is observed, however it does not reflect the velocity of growth but is a proof of it's important role in this period (Ojeda, Jameson 1977).

Functional development of the sheep somatotropic axis is completed after about 12 weeks of age and is independent of the photoperiod (Wańkowska et al. 2008b). In female lambs GH secretion decreases from early to late infancy (5–12 weeks of life). Weak ovariectomy effect on GH secretion during the rearing period proves the development of the feedback mechanism in the somatotropic axis of infantile lambs (Wańkowska et al. 2012). Somatostatin becomes the main factor regulating GH secretion during transition from early to middle infancy (from 5 to 9 weeks of age) (Wańkowska et al. 2012). Strong, inhibiting impact of somatostatin lasts to the 22 week of the lambs life and leads to diminished GH release (Wańkowska et al. 2008b). The mode of action of gonadal factors on GH secretion in lambs is through the suppressive effect of somatostatin, and this action decreases at the beginning of the juvenile period (Wańkowska et al. 2012). In male lambs, testicular hormones stimulate GH secretion from the neonatal to pubertal period. Similarly to female lambs the influence of gonadal hormones on the somatotropic axis activity increases after weaning (Wańkowska 2012). As recently suggested (Wańkowska 2012; Wańkowska et al. 2012), GH seems to participate in the control of ovine gonads development during the juvenile period of ontogeny.

Numerous changes in the regulation of offspring's growth appear during the postnatal ontogeny. Maturation of the feedback mechanism within the somatotropic axis caused by increasing impact of gonadal factors is a key process controlling growth and onset of puberty (Wańkowska 2012; Wańkowska et al. 2012).

Gonadotropic axis secretory activity during the rearing period and onset of puberty

The main function of the HPG axis is to regulate reproduction. Gonadotrophin-releasing hormone (GnRH) is synthesized in the hypothalamus and stimulates the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion in the pituitary gland. Gonadotrophins potentiate synthesis of the estrogens and progesterone, which influence ovary follicle development. Furthermore, LH and FSH enhance androgens secretion, which are overriding hormones in spermatogenesis.

Activity of the HPG axis changes during the postnatal ontogeny and depends on many factors. Pivotal elements influencing the HPG axis activity are gonadal hormones as an internal environmental factor (Jansen 1982; Veldhuis et al. 2006; Wańkowska et al. 2008a; Wańkowska et al. 2010a; Wańkowska et al. 2010b) and keeping and later mother-infant ties interruption as an external environmental factor (Wańkowska, Polkowska 2006).

In rats pituitary gland, populations of LH and FSH containing cells and the amount of mRNA for both hormones increases gradually from the infantile to juvenile period. In the next stages only the number of LH containing cells increases until puberty (Jansen 1982).

In the infantile sheep, the activity of the HPG axis, manifested by the secretion of LH and FSH, is increased. The growing and mostly inhibiting impact of ovarian factors on the gonadotrophic hormones secretion in sheep is observed during the functional development of the HPG axis (Wańkowska et al. 2010a). Diminished plasma concentration of LH in the infantile period is necessary for morphological and functional development of ovaries before gonadal maturation (Wańkowska et al. 2010a). In the juvenile period, plasma LH and FSH levels increase as a result of the estrogen negative feedback declining (Wańkowska et al. 2010a). During the rearing period a high activity of the HPG axis is observed in male lambs. A decreased activity of the HPG axis in the next developmental stages is the result of the increasing importance of testicular hormones in the regulation of gonadotrophins secretion. In lambs, the feedback mechanism of testicular hormones is fully developed in the period preceding puberty (in 12 weeks of age) (Wańkowska et al. 2010b).

In animals with short-term ontogeny like rodents, systematic enhancement of the HPG axis activity finally leads to puberty (Jansen 1982). In animals with long-term ontogeny like sheep, frequent changes in populations of gonadotrophes in the pituitary gland appear, which reflect the secretory pattern of LH and FSH (Wańkowska et al. 2010a; Wańkowska et al. 2010b).

Interactions of the HPG and somatotropic axis

Processes of growth and reproduction are closely related. Physiological connections between the HPG and the somatotropic axis are basis for their interactions. In the hypothalamus of rodents physical connections between the somatostatinergic and GnRH neurons was shown (Bhattarai et al. 2010; Koyama et al. 2012). It was further observed that somatostatin not only inhibits the GH secretion, but also decreases the activity of the GnRH neurons. Several findings also indicate the ability of somatostatin to regulate GnRH neurons function (Bhattarai et al. 2010; Koyama et al. 2012).

Colocalization of the hypothalamic neurons synthesizing the somatostatin and GnRH as well as the estrogen receptor α (ERα) expression in somatostatinergic neurons (Scanlan et al. 2003) seems to be an important aspect of interactions between both axes (Bhattarai et al. 2010; Koyama et al. 2012).

In adult sheep, 70% of perikarya in the ventromedial nucleus (VMN) and 13% of perikarya in the ARC that synthesize somatostatin express ERα. Estrogen receptor α plays a prominent role in the transmission of preovulatory signals (Scanlan et al. 2003). Somatostatin intracerebral infusions resulted in decreased GnRH and LH release in sheep. Additionally, it is assumed that somatostatin may be involved in the signal transduction induced by estradiol feedback to GnRH neurons in the preoptic area in adult sheep (Pillon et al. 2004).

Our findings in sheep indicate that the gonadal factors modulate mechanisms within the somatotropic axis in lambs before and after weaning to synchronize the somatic growth with gonadal development (Wańkowska 2012; Wańkowska et al. 2012).

Biology of stress

Stress is the organism's reaction to the stressor resulting in physiological and/or behavioral changes in the multiple functions of the body. The appearance of physical or psychoemotional stress factors mobilizes the hypothalamus directly or indirectly to activate the autonomic and/or endocrine cascades of the stress response (McEwen 2000).

Physiological response to stress factors is associated with the activation of the autonomic nervous system sympathetic-adrenomedullary (SAM) and the HPA axis (McEwen 2000). The SAM system is responsible for fight/flight reactions and is activated in the first seconds after risk onset. The SAM system is responsible for synthesis and release of catecholamines adrenaline and noradrenaline, which mobilize the organism to rapid metabolic changes and physical activity (Mitra, Sapolsky 2009).

Activation of the HPA axis is delayed and its effects persist longer than the SAM system. The HPA axis interacts with higher levels of the nervous system. The pivotal modulators of the HPA axis are corticotropin-releasing factor (CRF) and arginine-vasopressin (AVP) which are released from the PVN of the hypothalamus. In the anterior pituitary gland CRF and AVP stimulate the adrenocorticotropic hormone (ACTH) release, which positively influences glucocorticoid secretion (cortisol, corticosterone) in the adrenal cortex. Among important functions of glucocorticoids are generation of glucose sources through protein degradation by hepatic gluconeogenesis, increase of the lipolysis and energy mobilization from fatty acids.

Evolution has provided additional physiological mechanisms of the stress reaction to ensure proper adaptation of the organism to stress conditions. The hypothalamus has a direct neural pathway with the adrenal medulla. Activation of the hypothalamus causes adrenal medulla stimulation and extra secretion of adrenaline and noradrenaline, which reinforce the function of the SAM system (McEwen 2000).

The stress reaction involves other centers, systems and structures of the brain. These include the locus coeruleus, which additionally activates the SAM system, the dopaminergic system responsible for the modulation of emotional responses and learning, serotoninergic system associated with depression, aggressive behavior and anxious feelings and the hippocampus playing a key role in memory processes. All of these systems participate in the modulation of the HPA axis function (Vermetten, Bremner 2002; Mitra, Sapolsky 2009).

The hypothalamic-pituitary-adrenal axis activity during maternal deprivation

Maternal deprivation influences offspring's HPA axis function (Fig. 1). In young rats, separation from the mother activates the HPA axis, which is expressed by increased plasma concentration of ACTH and glucocorticoids (Levine, Wiener 1988). Neonatal mother-offspring ties interruption resulted in decreased amount of mRNA CRF in hypothalamus and increased level of mRNA of GR in hippocampus of young rats (Liu et al. 1997).

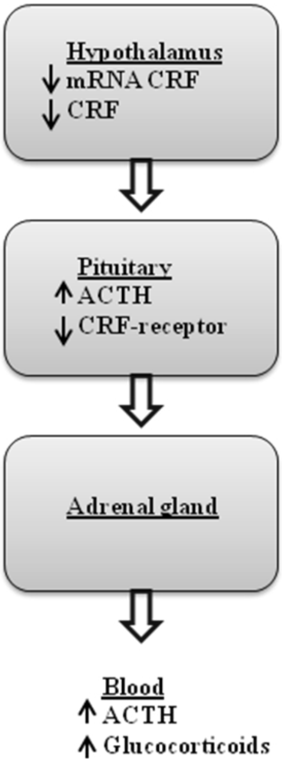

Figure 1. The effect of the maternal deprivation on the HPA axis activity in rodents and sheep during ontogeny (Levine, Wiener 1988; Pihoker et al. 1993; Plotsky, Meaney 1993; Liu et al. 1997; Sevi et al. 1999; Wańkowska et al. 2006; Chen et al. 2012; Lajud et al. 2012). Increased ↑ ; Decreased ↓ amount or concentration of the chosen components of the HPA axis

A different response of the HPA axis was shown to be dependent on the age of rats subjected to maternal separation. No changes in the pituitary sensitivity to CRF, and a decreased amount of CRF in the hypothalamus were observed after a 24-hours separation from the mother in 10-day-old rats. However, in the same experimental design, no changes in the hypothalamus CRF and a diminished amount of the CRF receptor in the pituitary gland were noted in 18-day-old rats (Pihoker et al. 1993).

Numerous studies clearly suggest the influence of neonatal handling on neuroendocrine responses in adult life. Greater sensitivity of the HPA axis was shown in rats subjected to maternal separation in response to the subsequent stressful experiences (Levine et al. 1991). In female adult rats which experienced maternal separation the changes in all researched markers of HPA axis activity (corticosterone levels, CRF mRNA levels in the PVN and glucocorticoid receptor density in the hippocampus) was observed (Aisa et al. 2008). Rats subjected to maternal separation between 2 and 13 days of life showed a higher synthesis of mRNA CRF in the hypothalamus in adulthood (Plotsky, Meaney 1993; Chen et al. 2012). In plasma of adult rats which neonatally experienced maternal separation elevated basal and stress-induced corticosterone levels were observed (Lajud et al. 2012).

In maternally deprived mice, time dependent activation of the HPA axis was observed. At first an increased plasma concentration of ACTH was noted, and next an increased plasma concentration of corticosterone was observed. The highest HPA axis activity connected with the enhancement of cortisol and ACTH release occurred between 4 and 8 hours after separation from the mother. However, after 12 hours of maternal separation the concentration of the HPA axis hormones fell, which was connected with the activation of feedback mechanisms (Schmidt et al. 2004).

Social isolation is supposed to cause the strongest reactions of the HPA axis of offspring in the studies concerning the impact of psychoemotional stressors on cortisol secretory activity in lambs (Mears, Brown 1997). Likewise, increased cortisol release was shown in lambs subjected to early maternal deprivation (Sevi et al. 1999). Furthermore, in lambs weaned at 12 weeks of age an increased release of CRF from the nerve terminals in the median eminence and accumulation of ACTH in the pituitary gland were observed (Wańkowska et al. 2006). Cieślak et al. (2015) showed a sex-dependent differences in cortisol secretion in lambs subjected to maternal deprivation. In female lambs maternal deprivation caused the stimulation of cortisol secretion in all examinated periods (9^{th}, 12^{th}, 16^{th} week of life). In male lambs stimulating effect of the maternal deprivation in 9^{th} week of life has changed on inhibiting impact in 12^{th} and 16^{th} weeks of life (Tab. 1).

In summary, early maternal deprivation influences the HPA of young mammals. Observed changes differ depending on the species, age or sex of maternally deprived animals. Effects of maternal deprivation may persist for a long time and have consequences in subsequent stages of mammalian life (Levine et al. 1991; Plotsky, Meaney 1993; Aisa et al. 2008; Chen et al. 2012; Lajud et al. 2012).

Somatotropic axis activity during maternal deprivation stress

Available data confirms the impact of stress factors on the somatotropic axis functions in the offspring. An increased number of somatostatin immunoreactive cells in the hypothalamus and decreased GH secretion in maternally deprived rats was shown (Juarez et al. 1988). Kuhn et al. (1990) also observed a diminished plasma GH level in rats subjected to maternal separation. This change however was reversible and after reuniting the offspring with the mother, plasma GH of young rats reverted back to the initial level. Furthermore, Katz et al. (1996) noted that overstimulation of the serotonin neurons caused the reduction of GHRH neurons activity of the hypothalamus and finally leads to diminished GH secretion during maternal separation.

It was observed that low plasma GH concentration during maternal separation stress in rodents may influence growth. In maternally deprived infantile rats, somatic growth indicators such as: body weight, nose-rump length, tail length and head length were defined. Moreover all tested parameters of growth were decreased (Dhungel 2007). Additionally, a decreased daily weight gain in rats subjected to interruption of mother-offspring ties was shown (Jurcovicova et al. 1998; Barreto et al. 2013).

Similarly to rats, maternal deprivation affects the somatotropic axis in sheep. The short-term effect of weaning involves enhancement of GH secretion via restraining of somatostatin output in lambs (Polkowska, Wańkowska 2010). In the response of the somatotropic axis of lambs subjected to maternal deprivation sex-dependent differences were noticed. In plasma of female lambs subjected to maternal deprivation stress increased concentration of GH in 9 weeks of life and the fall of concentration in 12 week of life was observed. In male lambs the stimulus effect of the maternal deprivation on GH secretion has been maintained until 12 weeks of life. After this period decreased secretion of GH was observed (Tab. 1) (Cieślak et al. 2015).

Summarizing, in rats during stress of maternal deprivation GH secretion is diminished (Juarez et al. 1988; Kuhn et al. 1990). However, there is not enough data considering the somatotropic axis function during the maternal deprivation in the other species to draw unequivocal conclusions (Polkowska, Wańkowska 2010). However it is hypothesized, that among others players CRF, which decreases GH secretion *in vitro* could link stress and growth processes (Colao et al. 1994). Furthermore, neuropeptide Y (NPY) which is also released in stress conditions, and which neurons were colocalizated with the somatostatin neurons (Iqbal et al. 2005), seems to modulate the somatotropic axis function during maternal deprivation (Polkowska, Wańkowska 2010).

Influence of the maternal deprivation on the HPG axis activity

Numerous reports describe the impact of physical and psychoemotional stress on the HPG activity in mammals (Warren, Fried 2001; Genazzani 2005; Wańkowska et al. 2006; Wańkowska, Polkowska 2010). The effect of stress is prominent on the pituitary gland level (Wańkowska et al. 2006; Fathollahi et al. 2013). Stress may influence gonadotrophin release by modification of the GnRH secretion, by changes of GnRH receptor numbers in the pituitary cells or by influencing estrogen feedback mechanisms (Brann, Mahesh 1991; Wańkowska, Polkowska 2010).

The short-term effect of maternal deprivation in lambs involves the changes in secretion of gonadotrophic hormones in the pituitary due to restraining of GnRH output (Wańkowska et al. 2006; Wańkowska, Polkowska 2010; Polkowska, Wańkowska 2010). In male lambs subjected to maternal deprivation diminished LH secretion during all examinated periods (9, 12 and 16 weeks of age) was observed. Inhibiting impact of the maternal deprivation on the LH secretion in female lambs started at 12 weeks of age and pertained to 16 weeks of age. Secretion of the FSH was increased in male lambs after maternal deprivation in all examinated periods, furthermore in female lambs subjected to maternal separation diminished FSH secretion was observed in 9 weeks of age and increased FSH concentration in 12 an 16 weeks of age was noted (Tab. 1) (Cieślak et al. 2015).

Table 1. The schematic presentation of the cortisol, GH, LH and FSH secretory pattern during the postnatal transition to puberty in lambs subjected to maternal deprivation (Cieślak et al. 2015). ↑ Stimulation; ↓ Inhibition, = No effect on hormone secretion

	9 weeks of life		12 weeks of life		16 weeks of life	
	♀	♂	♀	♂	♀	♂
Cortisol	↑	↑	↑	↓	↑	↓
GH	↑	↑	↑	↓	↓	↓
LH	=	=	↓	↓	↓	↓
FSH	↓	↑	=	↑	↑	↑

There are not many data describing functioning of the HPG axis during the maternal deprivation. Existing data however demonstrate the responsiveness of the HPG axis of adult sheep subjected to psychoemotional stress (Przekop et al. 1988; Polkowska, Przekop 1992). Examination of the effect of timedepending, footshock stress in the adult anestrous sheep revealed the increased GnRH accumulation in the median eminence and the medial preoptic area (MPOA). This may indicate for the suppression of the release processes in the response to stressor (Przekop et al. 1988).

The data concerning the impact of maternal deprivation on the HPG axis activity in other species is scanty. In male rodents maternal separation altered peripubertal testosterone secretion (Bodensteiner et al. 2014). Available data, however, shows a high vulnerability of the HPG axis to stress conditions in young and adult animals.

Summary

Studies on the determination of the effect of the maternal deprivation on rodent offspring physiology and behavior which have started in the 50's have contributed to the development of this field of research in the next decades. There is a lot of data focused on the influence of maternal separation on behavior and the HPA axis activity of young rodents during separation and in their later life. However, data describing the impact of maternal deprivation on the functioning of pivotal hormonal axes involved in growth, development and puberty in rodents and in other species are scarce. In particular, there is a need to perform experiments on domestic animals. Obtained results could be a source of information about the mechanisms underlying effects of maternal separation on the somatotropic and the HPG axis function in which are believed to be closer to human physiology than rodents.

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WPŁYW MATKI NA AKTYWNOŚĆ WYDZIELNICZĄ UKŁADU PODWZGÓRZE-PRZYSADKA-NADNERCZA, UKŁADU PODWZGÓRZE-PRZYSADKA-GONADY ORAZ UKŁADU SOMATOTROPOWEGO POTOMSTWA W TRAKCIE POSTNATALNEJ ONTOGENEZY

Streszczenie

W trakcie odchowu przy matce, większość procesów fizjologicznych młodego ssaka znajduje się pod kontrolą matczyną. Oznacza to, że matka znosi wpływ czynników środowiska zewnętrznego na rozwijające się potomstwo. Przerwanie odchowu przy matce aktywuje układ podwzgórze-przysadka-nadnercza (z ang. *hypothalamus-pituita-*

ry-adrenal, HPA) młodego ssaka dzięki czemu rozwijający się organizm adaptuje się do nowych okoliczności. Uważa się, że zbyt wczesne zerwanie więzi matka–potomek aktywuje nie do końca dojrzały układ HPA i zmienia funkcje innych układów hormonalnych rosnącego organizmu. Ten artykuł przeglądowy opisuje zmiany w aktywności wydzielniczej układów somatotropowego oraz gonadotropowego u gryzoni oraz owiec w trakcie odchowu przy matce oraz po przerwaniu odchowu przy matce, które w postnatalnej ontogenezie zwierząt uważane jest jako wydarzenie stresujące. Ponadto, skupiono się na zmianach w aktywności wydzielniczej układu HPA młodych zwierząt poddanych matczynej separacji.

Słowa kluczowe: ontogeneza postnatalna, osiągnięcie dojrzałości płciowej, stres wczesnego przerwania odchowu przy matce, wzrost

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