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Interactions Between Reproductive and Immune Systems During Ontogeny: Roles of GnRH, Sex Steroids, and Immunomediators

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1. Introduction

Reproduction is an essential function of every animal species, and its realization depends on a complex of interrelated neural, endocrine, immune, and behavioral reactions. It is now accepted that the neuroendocrine system (including its reproductive component) and the immune system have a reciprocal regulatory influence development and functioning during pre- and postnatal ontogeny (Watanobe & Hayakawa, 2003; Zakharova et al., 2005; Carreras et al., 2008; Li et al., 2007; Chapman et al., 2009; Wu et al., 2011). The functions of these systems change during ontogeny. In the perinatal period, they are involved not only in regulatory but also in morphogenetic processes, unlike in the postnatal period. The tight bilateral connection between these systems is of special significance during the early, critical period of ontogeny, when the functions necessary for postnatal life of newborns are being established. The key role in the interaction of the reproductive and immune systems is played by the hypothalamic neuropeptide gonadotropin-releasing hormone (GnRH) and sex hormones. During the perinatal period, they regulate the growth and differentiation of various fetal tissues, including the lymphoid tissue. In postnatal life, the dynamics of endocrine processes related to reproduction are regulated by the level of GnRH secretion into the hypothalamo-pituitary portal circulation. GnRH regulates secretion of pituitary gonadotropins, which regulate secretion of sex hormones. GnRH is also involved in regulation of sexual behavior, transmission of olfactory signals, and control of humoral and cell-mediated immunity. Sex hormones, in turn, regulate GnRH production in the hypothalamus (and, therefore, secretion of pituitary gonadotropins) and also its production in the thymus and spleen (Azad et al, 1998; Hrabovszky et al., 2000). On the other hand, immune system mediators such as thymic peptides and proinflammatory cytokines have a role in controlling the development and functioning of the reproductive system.

Interactions of the reproductive and immune systems during early ontogeny are prerequisite to their normal functioning in adult life. Changes in the normal levels of GnRH and sex steroids in the developing fetus or newborn and their exposure to adverse environmental factors cause disturbances in long-term programming of the regulatory mechanisms of both reproductive and immune systems (Jacobson et al., 2000; Razia et al., 2006; Cameron et al., 2008; Champagne & Curley, 2008). The brain is especially sensitive to perinatal programming by sex steroids, which not only contribute to the patterning of brain

structures during early ontogeny but also activate sexual behavior in prepubertal and pubertal males and females. Thus, the brain retains its plasticity for programming at later stages of ontogeny, being most responsive to sex steroids in adolescence as well as in the perinatal period (Shulz et al., 2009). The formation of individual structural–functional elements of the reproductive and immune systems and the establishment of relationships between them are not strictly genetically controlled. These processes are characterized by high functional lability and sensitivity to various regulatory factors, which provides the possibility of correcting disturbances in the reproductive process.

2. Effect of the reproductive system on the immune system: Roles of GnRH and sex steroids

Distinctive features of GnRH-producing neurons include their small population size (800–2000 cells), diffuse distribution in the septo-preoptic hypothalamic region, and extracerebral origin during ontogeny. Most these neurons have axons terminating in the median eminence, where GnRH is released in the portal circulation and regulates the synthesis and secretion of the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by gonadotrope cells. GnRH isolated from the mammalian brain was initially regarded only as the hormone controlling the reproductive function, but subsequent studies have demonstrated that GnRH occurs in a variety of functionally different forms. To date, 23 such forms have been identified in vertebrates. Three of them—GnRH1, GnRH2, and GnRH3—are the most frequent, being expressed in groups of neurons differing in origin, location, and functional role. In adult animals, GnRH1 is expressed mainly in the hypothalamus; GnRH2, in the midbrain and tectum; and GnRH3, in the rostral regions of the forebrain. The population of hypothalamic neurons expressing GnRH1 is usually referred to as the GnRH1 system, and its basic function is to regulate the release of gonadotropins. GnRH2 and GnRH3 supposedly function as neuromodulators, the former being involved in the regulation of sexual behavior and the latter, in the integration of olfactory signals and other processes related to reproduction. Extracerebral synthesis is characteristic mainly of GnRH2, which has been revealed in the thymus, spleen, ovaries, testes, prostate, mammary gland, and placenta (Jacobson et al., 2000; Zakharova et al., 2005). Along with hypothalamic GnRH, extracerebral GnRH2 plays a role in the development and functioning of the immune system at different stages of ontogeny (Morale et al., 1991; Zakharova et al., 2005). According to Marchetti et al. (1998), GnRH is one of the most important signal molecules involved in the neuroendocrine–immune interaction.

Sex steroids, in turn, control the development and functioning of the hypothalamo-pituitary and immune systems. In particular, they account for the programming of sexual dimorphism in the structure and functions of the hypothalamo-pituitary system of vertebrates and regulate GnRH production in the hypothalamus and expression of GnRH receptors in the pituitary, thereby modulating the response of gonadotrope cells to this hormone. Sex steroids also modulate the molecular processing of GnRH in the thymus and its concentrations in the thymus and spleen (Azad et al, 1998).

The effects of these hormones on the immune and endocrine systems apparently differ depending on the period of ontogeny, as is the case with many other factors. During the early period, they cause long-lasting or irreversible changes in the structure and functions of the above systems, whereas their effects in adult animals are short-term and reversible.

2.1 Role of GnRH in immune system development and functioning at different stages of ontogeny

The involvement of GnRH in the differentiation of lymphocytes and regulation of immune response is lifelong. Its neonatal administration in normal mice accelerates the development of immune reactions (Marchetti et al., 1989). In rats and monkeys, central or peripheral blockade of the GnRH receptor antagonists in the neonatal period leads to reduction of mature T- and B-lymphocyte counts in the thymus, spleen, and circulating blood and suppression of antibody production and mitogen-induced proliferative response of T cells, with the immune reactions returning to the norm only by the age of 3 months in rats and 5 years in monkeys (Morale et al., 1991). Thymic and splenic lymphocytes differ in sensitivity to GnRH. Neonatal administration of a GnRH antagonist in rats results in complete block of the mitogen-induced proliferative response of thymocytes, whereas this response of splenocytes is blocked only partially. GnRH and its agonists prevent age-related involution of the thymus and normalize the suppressed functional activity of thymocytes (Marchetti et al., 1989). In pregnancy, the functional activity of GnRH in controlling the numbers of thymocytes is suppressed due to the intensified synthesis of prohibitin, an antiproliferative protein; as a consequence, the maternal thymus undergoes involution. The suppression of T-lymphocyte development in pregnancy is an adaptation against allogeneic fetal rejection. Administration of an GnRH agonist results in normalization of thymocyte count (Dixit et al., 2003).

There is evidence that GnRH exacerbates progression of autoimmune diseases. In particular, this follows (by contradiction) from the data by Jacobson et al. (2000) that administration of an GnRH antagonist to New Zealand mice with systemic lupus erythematosus leads to a drop in the levels of both total IgG and anti-DNA antibodies, relief of disease symptoms, and extension of life span, with these effects being observed in both intact and castrated animals of both sexes. It should be noted that the diseases progresses more severely in females than males, which the authors attribute to sex-related differences in the expression of GnRH receptors or G protein (Jacobson et al., 2000). Although the available data on the involvement of GnRH in immune response modulation and exacerbation of autoimmune diseases in adults are fairly abundant, its role in these processes is not yet completely clear. However, since the functions of many hormones in postnatal life are aimed at the maintenance of immune system homeostasis in response to changes in ambient conditions (Dorshkind & Horseman, 2000), such a function cannot be excluded for GnRH.

According to our data (Zakharova et al., 2000), GnRH becomes involved in the regulation of T-cell immunity as early as during prenatal ontogeny. Surgical ablation of the hypothalamus (encephalectomy) *in utero* in 18-day rat fetuses results in 30–40% suppression of concanavalin A (Con A)-induced response in thymocytes isolated on day 22, but intraperitoneal injection of GnRH (0.2 μg per fetus) immediately after surgery restores this response to the norm. No such effect has been observed in experiments with sham-operated fetuses. Moreover, GnRH (10^{-9} and 10^{-7} M) added to a culture of thymocytes from encephalectomized fetuses has proved to enhance their Con A-induced proliferative response in a dose-dependent manner. The involvement of GnRH at early stages of immune system development is also confirmed by the results of experiments on central or peripheral blockade of the synthesis of GnRH or its receptors in rat fetuses (Zakharova et al., 2005). On day 20 of pregnancy, fetuses in one uterine horn were intraperitoneally injected with either the selective GnRH antagonist D-pGlu-D-Phe-D-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2 or anti-GnRH antibodies, and fetuses in the other horn, with 0.9% NaCl solution or nonimmune rabbit serum. The GnRH antagonist (2 μg per fetus) caused 40–50%

suppression of Con A-induced proliferative response of thymocyte on day 22, compared to that in fetuses injected with saline (0.9% NaCl). It should be noted that this response did not differ between male and female fetuses, either in the norm or after the antagonist injection. When thymocytes from 22-day fetuses were cultured in the presence of the GnRH antagonist (10^{-5} or 10^{-6} M), no such decrease in the proliferative response was observed. In the case of injection with anti-GnRH antibodies, Con A-induced proliferative response of thymocytes was suppressed fivefold, compared to that in fetuses injected with either saline or nonimmune serum.

On the other hand, the injection of a long-acting GnRH agonist to prepubertal female mice has been found to suppress T- and B-cell maturation in the primary lymphoid organs. It appears that GnRH acts on lymphocyte precursors so that changes in its initial concentration lead to suppression of their differentiation in the central organs of the immune system (the thymus and bone marrow), which, in turn, accounts for the decreased numbers of differentiated T and B cells in spleen, a secondary lymphoid organ (Rao et al., 1995).

The synthesis of GnRH and its receptors in the thymus and spleen of adult animals has been confirmed experimentally. As shown by Azad et al. (1997), the *Jurkat* human leukemia T-cell line (phenotypically similar to normal human T lymphocytes) expresses GnRH mRNA and secretes this hormone and its precursor into the culture medium. The proliferative activity of these cells increases under the effect of either endogenous or exogenous GnRH, whereas its antagonist suppresses their proliferation. According to the same authors (Azad et al., 1998), the concentration of GnRH in the thymus significantly increases in castrated rats, but this increase is prevented by testosterone injection. It is considered that sex steroids modulate molecular processing of the GnRH precursor, with its processing in the thymus differing from that in the hypothalamus.

The results of our experiments exhibit that GnRH is also synthesized in the fetal thymus (Zakharova et al., 2005). Immunocytochemical analysis for GnRH in the thymus of 21-day rat fetuses revealed the presence of GnRH-positive cells morphologically identical to thymocytes. Quantitative assessment of GnRH in the thymus exhibited that its content was minimal in 18-day fetuses, increased by a factor of about 1.5 in 21-day fetuses, and further increased by postnatal day 3 (by 65 and 40%, compared to intrauterine days 18 and 21), reaching the level characteristic of the hypothalamus. The GnRH contents in the thymus were similar in males and females. A considerable GnRH level was also detected in the blood serum of rat fetuses. It reached a peak in 18-day fetuses and decreased by half in 21-day fetuses, remaining fairly high relative to those in the thymus and hypothalamus. After surgical ablation of the hypothalamus (encephalectomy) on intrauterine day 18, the concentrations of GnRH in the thymus and peripheral blood of 21-day fetuses, either male or female, was half as low as in sham-operated fetuses. The origin of circulating GnRH is as yet unclear. Since its level drops after encephalectomy, it appears that at least half its amount is of brain origin and, therefore, the level of this hormone at the periphery is controlled by the hypothalamus. It cannot be excluded, however, that GnRH found in the circulating blood of fetuses comes from other sources (e.g., the placenta).

All the above data suggest that GnRH can control the development and functioning of the immune system via the hypothalamo-pituitary axis and is involved in an autocrine or paracrine regulation of the immune response during postnatal life. There are several possible mechanisms of GnRH action on the immune system: it can interact with specific receptors on thymic epithelial cells that synthesize peptides participating in T-cell

maturation, as well as directly interact with such receptors on lymphocytes. In addition, GnRH can induce both the expression of interleukin (IL)-2 receptors on lymphocytes and the synthesis of gamma-interferon (IFNγ), which, in turn, induces IL-2 production by T cells, thereby regulating their numbers (Grasso et al., 1998).

2.2 Role of sex steroids in the development of immune and endocrine systems

During early ontogeny, sex hormones (along with other hormones) participate in the development of the hypothalamo-pituitary and immune systems. It is known that exposure of the fetus to adverse factors can affect the structural and functional programming of these systems, with consequent disease susceptibility in adulthood (Langley-Evans, 2006). Alterations in a certain developing system usually entail alterations in other systems. External factors such as stress, treatment with pharmaceuticals, and mother's inadequate diet and behavior during pregnancy and breast feeding place the fetus (newborn) at risk for autoimmune, allergic, metabolic, nervous, and mental disorders in later life (Fowden & Forhead, 2004; Wang et al., 2009; Wu et al., 2011).

A strong stimulus changing homeostasis of the fetus is exerted by sex steroids. The mechanisms of sexual differentiation of the brain were addressed even in the first studies on prenatal programming of the GnRH system. It has been shown long ago that the development of the brain in male mammals initially follows the female pattern, but specific brain regions in a certain period of ontogeny are influenced by testosterone aromatized into estradiol, which leads to masculinization of the brain and its subsequent development according to the male scenario. This period is critical for organization of the GnRH system, and its timing varies between species. In rodents, brain masculinization takes place during the late intrauterine–early postnatal period; in guinea pigs, during midpregnancy; in rhesus monkeys and humans, this process is accomplished by the second trimester of pregnancy; whereas in sheep it continues from days 30--37 to 147 of intrauterine development.

An increase in the concentration of androgens in mice between intrauterine day 18 and postnatal day 14 causes changes in the development of the hypothalamo-pituitary system. Male transgenic hCGαβ+ mice overproducing human chorionic gonadotropin are characterized by an elevated GnRH level in the hypothalamus, a reduced FSH level in the pituitary and circulating blood, and inhibited expression of the mRNA of receptors for GnRH and estrogens in the pituitary (Gonzalez et al., 2011). The sexual behavior of a pregnant female has an effect on the functioning of the endocrine system in its offspring, which is mediated by epigenetic modifications at the promoter for oestrogen receptor alpha (ERα) and subsequent effects on gene expression (Cameron et al., 2008). Estradiol and testosterone injected to female mice during the neonatal period induce the development of infertility, whereas their injection on postnatal day 7 causes no disturbances in the reproductive system. Hydrocortisone injected together with estradiol prevents the development of infertility (Chapman et al., 2009).

Sex hormones also modulate the development of lymphoid organs, the thymus being their main target in the immune system. The drop in the level of sex hormones in male mice after pre- or postpubertal castration causes thymic hypertrophy (with increase in thymocyte count) and enhancement of graft rejection reaction. The phenomenon of twofold increase in thymus weight in castrated males was discovered more than a century ago, but its mechanism has not yet been elucidated in detail. Injection of androgens to castrated animals results in a rapid decrease in thymus weight, with signs of active apoptosis being observed

in the organ. The effects of androgens are realized via traditional receptor-mediated mechanisms (Olsen et al., 1996). Receptors for estrogens and androgens in the thymus are expressed as early as during embryonic development, with their level increasing by birth (Staples et al., 1999). Thymocytes carry the same numbers of functional androgen receptors as do target cells for these hormones in the reproductive system, with the least mature thymocyte subpopulations being the richest in such receptors. The thymic stroma also expresses androgen receptors. Estrogen receptors are expressed on mature peripheral T and B lymphocytes, which mediate the immunomodulatory effects of sex hormones (Tanriverdi et al., 2003.

Injection of testosterone, estrogen, or their derivatives to chick or quail embryos results in atrophy of the bursa of Fabricius, degeneration of lymphoid tissue in follicles and its substitution by fibrous tissue, and disturbances in the development of thymic stromal elements creating the microenvironment for lymphocyte maturation (Razia et al., 2006). In addition, excess sex steroids cause disturbances in mammal immune system. In particular, they suppress differentiation of regulatory and cytotoxic T cells in the thymus, with consequent increase in the numbers of immature lymphocytes in the circulation, and cause an impairment of negative selection mechanisms, which results in the formation of self-reactive T cells (Chapman et al., 2009). Estrogens also stimulate an increase in the numbers of self-reactive B lymphocytes and the level of circulating autoantibodies (Olsen & Kovacs, 1996; Tanriverdi et al., 2003). These data are in agreement with the observation that females, especially when pregnant, are more vulnerable to autoimmune diseases, compared to males. On the other hand, it has been noted that the level of testosterone in male mice genetically resistant to infectious diseases is maintained high after infection with bacterial (Salmonella enteritis) endotoxin, whereas this level in sensitive males dropped significantly on day 14 after infection (Zala et al., 2008).

Female mice kept at high density in the presence of only one male in the cage become aggressive, unresponsive to mating attempts and do not copulate. The aggressive behavior of females correlates with elevated levels of testosterone, corticosterone, and progesterone. Compared to female mice kept under standard conditions, the weight of their ovaries and adrenals is greater, while that of the thymus and uterus is smaller, and the lysis of corpora lutea in the ovaries is prolonged and incomplete. Supposedly, high corticosterone suppresses the activity of T lymphocytes normally involved in this process (Chapman et al., 2000).

Despite general similarity in the effects of male and female sex hormones on the thymus, the resultant changes in the composition of cell subpopulations in this organ are different: estrogens cause a decrease in the number of cortical T lymphocytes and an increase in the contents of more mature cell forms, whereas androgens have an opposite effect (Olsen and Kovacs, 1996).

Sex hormones also regulate the development of bone tissue and bone marrow and have an immunomodulatory effect on B lymphocytes in adults. Estrogens control differentiation of osteoclasts, mesenchymal stem cells, and myelopoiesis in the bone marrow (Carreras et al., 2008). Interacting with receptors on bone marrow stromal cells, sex hormones modulate B-cell differentiation. In either males or females, castration results in the increased numbers of pre-B cells in the bone marrow and mature B cells in peripheral organs, with the spleen growing in size (Olsen et al., 1996). In pregnancy, at a high estrogen background, the relative numbers of B lymphocytes in the bone marrow are decreased at almost all stages of differentiation (Tanriverdi et al., 2003).

Estrogens have a protective effect on the progression of autoimmune diseases, in particular, multiple sclerosis and autoimmune encephalomyelitis as its model. In pregnant women with multiple sclerosis, clinical remission is observed during the last trimester, at a high level of estrogens and progesterone; after delivery, this level drops, and the disease is exacerbated. Exogenous estrogens at physiological concentrations suppress the progression of experimental encephalomyelitis, supposedly by inhibiting the synthesis of proinflammatory cytokines (Van den Broek et al., 2005). The protective effect of sex steroids is dependent on a number of factors, including their dose and the age, sex, and metabolic pattern of animals. Thus, in NZB/NZW mice, which spontaneously develop lethal glomerulonephritis by the age of 8–14 months, castration of 14-day-old females accompanied by testosterone injection significantly prolongs their life span. On the other hand, castration and estradiol injection in males has an opposite effect. Moreover, males castrated at the age of 14 days die of this disease earlier than do males castrated at the age of 5 weeks, while castration of 14- to 15-week-old males has no effect on their life span.

It is noteworthy that the patterning of sexual behavior by sex steroids takes place not only during early ontogeny. As noted above, the brain retains its plasticity at later stages, and its responsiveness to sex steroids in males reaches a second peak during adolescence. Such a peak during the late postnatal period is also characteristic of females, but its exact timing has not yet been determined for them (Shulz et al., 2009).

2.3 Effect of immune system on the development of reproductive system: Role of cytokines and thymic peptides

Numerous data are available on the effect of the neuroendocrine system, including its reproductive component, on the establishment and functioning of the immune system. The immune system, in turn, is not only the target for hormones but is itself involved in the regulation of neuroendocrine system functioning. Mediators produced by the immune system have a role in programming the development of reproductive system in the fetus (Igaz et al., 2006; Li et al., 2007; Goya et al., 2004). The thymus is the central organ of the immune system, and its absence in homozygous athymic or neonatally thymectomized mice leads to severe disturbances in immune–neuroendocrine regulation. These disturbances manifest themselves not only in the inhibited functions of the immune system but also in the impaired synthesis and secretion of neuropeptides and hormones of the hypothalamus, pituitary, and peripheral endocrine glands (Goya et al, 2004; Chapman et al., 2009; Zakharova, 2009). The impaired neuroendocrine functions can be modulated by thymic peptides (Goya et al., 2007). There is evidence that bacterial endotoxins and proinflammatory cytokines have influence on the GnRH system of newborns (Li et al., 2007). In particular, neonatal activation of the immune system by these factors results in long-term sensitization of the adult GnRH system to the inhibitory effect of stress.

2.3.1 Regulation of the GnRH system in adult mammals

As noted above, GnRH has a modulatory effect on the development and functions of the neuroendocrine and immune systems, which, in turn, control the functioning of the GnRH system. It is through GnRH neurons that various neurotransmitters and neuropeptides (monoamines, gamma-aminobutyric acid, neuropeptide Y, opioids, tec.) and also cytokines convey signals from external stimuli influencing the state of the reproductive system (Karsch et al., 2002; Ciechanowska et al., 2007; Pereira A et al., 2010). Sex steroids are the

most powerful regulators of the GnRH system. During the estrous cycle, for example, the GnRH level in the anterior pituitary varies in antiphase to the level of plasma estrogens, with estradiol having been shown to reduce the content of GnRH mRNA in this pituitary region. On the other hand, estradiol increases the level of GnRH in the hypothalamus immediately before ovulation. It has long been considered that sex steroid exert their effect through steroid-sensitive sites of the brain, because no specific receptors have been found on GnRH neurons. However, this concept was questioned after identification of estrogen-sensitive regions in the promoter of human GnRH gene and estrogen receptors ERα and ERβ on cells of mouse GnRH neuronal cell line GT1-7 expressing the rat GnRH gene. Using improved techniques of in situ hybridization and binding of a radioactive estrogen analog, it has been shown that at least part of GnRH neurons in rats contain ERβ-receptor mRNA and can bind the radioactive estradiol analog (Hrabovszky et al., 2000). Estradiol and progesterone regulate the expression of receptors for GnRH on gonadotrope cells. Progesterone also regulates GnRH secretion depending on the physiological body state. Before ovulation, it activates GnRH neurons and stimulates its secretion. After ovulation, in the luteal phase of the estrous cycle, corpus luteum enhances progesterone synthesis in preparation for probable zygote implantation; under such conditions, progesterone inhibits the pulse secretion of GnRH.

Long-term studies on the complex pathways of sex steroid action on GnRH neurons have shown that they involve various neurotransmitter systems operating in different brain regions of adult mammals. In rodents, the main steroid-sensitive brain region is the preoptic area (anterior hypothalamus), including anteroventral periventricular, arcuate, and medial preoptic nuclei.

A major role in regulating the functional activity of GnRH neurons is played by catecholamines, primarily by dopamine and noradrenaline delivered by afferent fibers from the hypothalamic periventricular nucleus and brain stem. A long known fact is that noradrenaline coming from the brain stem is a "releasing factor" for the preovulatory GnRH surge. As shown in sheep, the noradrenergic neurons A1 and A2 projecting to the bed nucleus of stria terminalis carry receptors for estradiol and can directly or indirectly influence GnRH secretion (Pereira et al., 2010). It is also known that the seasonal inhibition of GnRH synthesis in the sheep hypothalamus is directly correlated with activation of dopaminergic neurons A15. The synthesis of dopamine by neurons of this group is intensified under the effect of gamma-aminobutyric acid (GABA)- and glutamatergic neurons of the ventromedial preoptic area and ventromedial and arcuate nuclei containing receptors for estradiol (Goldman et al., 2010). The majority of studies on the innervation of GnRH neurons by catecholaminergic terminals have been performed on rats and sheep Tillet et al, 1993). Using electron microscopy and stereotactic surgery, their authors have not only revealed the fact of such innervation but also made attempts to identify the origin of these catecholaminergic terminals. In rats, the noradrenergic system appears to innervate mainly the bodies of GnRH neurons in the septo-preoptic region, while the dopaminergic system innervates both the bodies of these neurons and their terminals in the organum vasculesum of lamina terminalis (OVLT) and median eminence. In sheep, unlike in rats, the bodies of GnRH neurons in the septo-preoptic region are innervated mainly by noradrenergic fibers from the locus coeruleus and brain stem, whereas their terminals in the median eminence are innervated by the dopaminergic system of the hypothalamus. Catecholamines exert their effect through receptors expressed on the surface of GnRH neurons (Hosny & Jennes, 1998).

As noted above, various neurotransmitters and neuropeptides (monoamines, neuropeptide Y, opioids, etc.) are involved in the transmission of signals from external stimuli that have an effect on the state of the reproductive system. Thus, long-term stress induced by electric shock results in the inhibition of GnRH expression in the hypothalamus, and this effect is jointly mediated by the opioidergic, noradrenergic, and serotonergic systems (Ciechanowska et al., 2007). It has been shown that steroid-dependent control of GnRH neurons is also accounted for by other factors, including GABA, somatostatin and kisspeptin (Pillon et al., 2004; Oakley et al., 2009).

Stimulation of the immune system by inflammatory bacterial endotoxins also inhibits the activity of the GnRH system in adult animals (Karsch et al., 2002). In the course of inflammation, immune system cells produce various pro- and antiinflammatory cytokines that activate the cascade of hormone secretion in the hypothalamo-pituitary system, thereby inducing the hormonal stress response. Bacterial endotoxins are often used in laboratory experiments as activators of the immune system. In particular, this concerns the lipopolysaccharide (LPS) from the outer membrane of Gram-negative bacteria, which is known as a factor stimulating the synthesis and secretion of pro- and antiinflammatory cytokines not only at the periphery but also in the CNS. Endothelial cells forming the hematoencephalic barrier have binding sites for LPS and its complex with accessory proteins (Singh & Jiang, 2004). Under the effect of LPS, these cells, along with cells of the immune system, can synthesize proinflammatory cytokines such as IL-1α, IL-1β, and IL-6; tumor necrosis factor alpha (TNFα); regulatory cytokine IL-10; and granulocyte/macrophage colony-stimulating factor (GM-CSF). Bacterial inflammation is also accompanied by an increase of another proinflammatory cytokine, the leukemia inhibitory factor (LIF) in the blood level, which penetrates the hematoencephalic barrier via a special transport system (Pan et al., 2008). Thus, bacterial inflammation stimulates signal transmission through vascular endothelium and cytokine transport through the hematoencephalic barrier. These cytokines act upon the GnRH system either directly or by inducing the synthesis or secretion of prostaglandins, neuropeptides, and catecholamines (Karsch et al., 2002).

Among cytokines mediating the effect of LPS on the GnRH system, the main role is played by IL-1β and TNFα. During bacterial inflammation, both these cytokines are almost equally effective in inhibiting the secretion of GnRH and, therefore, of the luteinizing hormone (Watanobe & Hayakawa, 2003). Injection of IL-1β into the rat brain ventricles markedly reduces both the synthesis of GnRH in the septo-preoptic region and the secretion of this hormone, which leads to disturbances of the estrous cycle (Kang et al., 2000). Moreover, IL-1β inhibits the expression of the c-fos protein in the nuclei of GnRH neurons, thereby altering GnRH synthesis during proestrus in rats. The role of IL-6 in GnRH secretion is as yet unclear. According to some publications, IL-6 inhibits the secretion of this hormone by neurons, whereas others conclude that IL-6 has no such effect even at high concentrations. However, it was shown, that LPS also stimulates the secretion of IL-6 in the preoptic area, which is followed by a drop in GnRH level within 30 min (Watanobe & Hayakawa, 2003). GM-CSF can also inhibit GnRH secretion in the mediobasal hypothalamic region by stimulation of GM-CSF receptors expressed on GABAergic neurons. Activation of these receptors leads to increased production of GABA, which influence on specific receptors on GnRH terminals and thereby inhibits NO synthase activity; as a result, the level of GnRH decreases (Kimura et al., 1997).

The direct involvement of proinflammatory cytokines in the regulation of GnRH secretion has been demonstrated on the model of the immortalized GnRH-expressing neuronal cell

line Gnv-4 derived from the rat hypothalamus. These cells have been shown to carry receptors for IL-1β and the accessory protein necessary for its activation as well as for the α chain of IL-6 and the β chain of oncostatin M, a functional analog of LIF participating in inflammatory processes (Igaz et al., 2006). Numerous data are also available on indirect effects of LPS and interleukins on GnRH secretion. In particular, it has been shown that IL-1β blocks nitric oxide (NO)-induced GnRH secretion in the mediobasal region of the hypothalamus, which, in turn, blocks the pulse secretion of the luteinizing hormone into circulation; as a result, the sexual behavior regulated by GnRH is suppressed (McCann et al., 2000). Similar to GM-CSF, IL-1β blocks GnRH release from the axons of GnRH by inhibiting NO synthase activity (Rettori et al., 1994). It also inhibits GnRH secretion induced by noradrenaline. Thus, in experiments with perfused fragments of the mediobasal hypothalamic region, the level of GnRH secretion proved to decrease when IL-1β was added to the incubation medium together with noradrenaline (Rettori et al., 1994). The suppression of GnRH secretion by LPS can also be mediated by opioids (He et al., 2003). Therefore, activation of the immune system in response to bacterial infection entails a complex of reactions in the neuroendocrine system that result in the suppression of female reproductive function.

2.3.2 Neuroendocrine and immune regulatory mechanisms in the development of GnRH system

During early embryonic development, GnRH neurons originate in the olfactory placodes, wherefrom they migrate rostrocaudally, toward the forebrain, along terminal, vomeronasal, and olfactory nerves. Entering the brain, these neurons reach their definitive location and begin to form axonal connections with circumventricular organs. The process of their migration to the brain can be divided into three stages: intramesenchymal migration from the olfactory placodes to the cribriform plate of the ethmoid bone, penetration through this plate into the brain, and intracerebral migration to the septo-preoptic hypothalamic region.

The general pattern of development of the GnRH system is common to most mammals, although the timing of formation and migration of its neurons varies between species depending on the duration of pregnancy and the degree of maturity at birth. In particular, GnRH neurons in mice are formed on day 11, and in rats, on days 12–14 of intrauterine development.

In the past two decades, many attempts have been made to reveal factors influencing the migration and differentiation of GnRH neurons. The main factors identified to date are the neural cell adhesion molecule (NCAM), which forms a substrate for migrating GnRH neurons, and peripherin, a member of the intermediate filament protein family (Fueshko & Wray, 1994). Disturbances of GnRH neuron migration caused by the absence of NCAM are responsible for the Kallmann syndrome in humans, which involves hypogonadism and anosmia. Other factors influencing the development of the GnRH system include chemoattractants and chemorepellents such as netrin, ephrin, and semaphorin 4D (Schwarting et al., 2007; Giacobini et al., 2008); neurotransmitters produced by the microenvironment of migrating GnRH neurons (GABA, serotonin, and catecholamines), which regulate the rate of their migration (Bless et al., 2000; Izvolskaia et al., 2009); and growth factors, including the fibroblast growth factor (FGF), brain-derived neurotrophic factor (BDNF), hepatocyte growth factor/scatter factor (HGF/SF), and LIF (Cronin et al., 2004; Chung et al., 2008).

The migration of GnRH neurons in the nasal region of rats is confined to the bundles of nerve fibers expressing polysialylated forms of NCAM (PSA-NCAM). Experiments on the removal of NCAM from this migration route (by gene knockout, enzyme treatment, or anti-NCAM antibodies) have shown that such disturbances entail significant reduction in the number of migrating neurons but do not completely block their migration. On this basis, it has been concluded that NCAM does not play the key role in the migration of GnRH neurons, although is involved in the formation of their migration route. Moreover, nerve fibers on the migration route of rat GnRH neurons in the nasal region also express other cell adhesion proteins, TAG-1 and CC-2. In mice, their migration in this region is connected with the bundles of nerve fibers expressing peripherin (Fueshko & Wray, 1994).

The development of the olfactory system proceeds with the involvement of numerous guiding molecules, in particular, chemoattractants, chemorepellents, and chemotrophic factors. The last group includes proteins such as Slit, semaphorins, and netrins, which provide directional and positional cues for growing axons of olfactory nerves and, supposedly, for GnRH neurons migrating in the nasal region and forebrain. The latter apparently pertains to netrins, a small family of secreted proteins involved in the formation of many nerve bundles in the brain. The receptor protein for netrins, DCC, has been identified and shown to be expressed in parallel to GnRH in normal mice and rats and also in mice with the DCC gene knockout. The DCC protein is present in peripherin-expressing nerve fibers guiding the migration of GnRH neurons in the nasal region, and its mRNA can also be detected in some GnRH neurons located in the nasal region but disappears after they enter the brain. Their migration in the nasal region is also guided by one more chemoattractant protein, HGF/SF, with its receptor protein (c-Met) being expressed in the immediate vicinity of migrating GnRH neurons (Giacobini et al., 2002).

The migration rate of GnRH neurons is regulated by neurotransmitters. Many neurotransmitters controlling the functions of the GnRH system in adults can also provide spatiotemporal cues to migrating GnRH neurons during development. In particular, penetration of these neurons to the forebrain is guided by GABA. GABAergic neurons found in the nasal region of mouse, rat, and human fetuses are derived from the epithelium of olfactory placodes, as are GnRH neurons. Their axons extend to the cribriform plate of the ethmoid bone, where they can interact with GnRH neurons located there. Injection of GABA receptor antagonists in pregnant mice retards the migration GnRH neurons (Bless et al., 2000). In chick embryos, a natural decrease in the rate of their migration in the zone of cribriform plate has been observed. The role of this phenomenon is unclear. It may be that the delay in migration is necessary for maturation of GnRH neurons or reorganization of their migration behavior prior to entering the forebrain. The migration of GnRH neurons in the forebrain is also guided by GABA. Injection of pregnant females with bicuculline, a GABA receptor antagonist, results in deviation of these neurons from the caudal segments of their migration route formed by peripherin-expressing fibers, with consequent disturbances in the pattern of their distribution in the forebrain (Bless et al., 2000).

Glutamate is another neurotransmitter producing an effect on the migration of GnRH neurons. Mechanisms of this effect in the nasal region and forebrain appear to be different. Blockade of AMPA glutamate receptors in mice retards penetration of GnRH neurons to the forebrain (Simonian & Herbison, 2001), but no such receptors have been found on these neurons in the nasal region. In the forebrain, the effect of glutamate is apparently mediated by a different type of receptors. This follows from the fact that GnRH neurons of mouse

fetuses have been found to contain NMDAR1 glutamate receptors and that prenatal blockade of these receptors accelerates the migration of GnRH neurons in the forebrain (Simonian & Herbison, 2001). The question as to the mechanisms of glutamate action on these neurons remains open.

The migration of GnRH-neurons to the definitive location in the septo-preoptic region is stimulated also by monoamines. Data on the distribution of GnRH neurons and the level of GnRH in the rostral brain region and hypothalamus of 21-day rat with chronic serotonin deficiency provide a basis for the conclusion that the migration of GnRH neurons is stimulated by serotonin (Pronina et al., 2001). The stimulating effect of serotonin is potentiated by testosterone, since it is better manifested in males than in females.

During the "preneurotransmitter" period of brain development, catecholamines function as highly effective morphogenetic factors influencing differentiation and migration of target cells. In mice, dopamine appears on day 10, and noradrenaline and adrenaline, on day 11 of embryonic development. In rats, the first neurons expressing tyrosine hydroxylase (TH) and catecholamines have been found on embryonic day 13 both in the midbrain and sympathetic ganglia. The migration of GnRH neurons to the forebrain in rats on embryonic days 16–18 coincides with the arrival of growing catecholaminergic afferent fibers to their target neurons in this brain region, i.e., with the appearance of an additional, local source of catecholamines. There is evidence that embryonic GnRH neurons and other topographically close neurons transiently expressing TH may also be involved in local metabolism of catecholamines.

According to our data, suppression of catecholamine synthesis in rat embryos by alpha-methyl-p-tyrosine (αMPT, a competitive TH inhibitor) beginning from day 11 of development leads to an increase in the number of GnRH neurons in the rostral segments of their migration route by day 17 and their accumulation in the zone of their entry into the forebrain by days 18–21 (Izvolskaia et al., 2009).

Experiments with double immunohistochemical labeling allowed us to determine the regions of interaction of the catecholaminergic brain systems with migrating and differentiating GnRH neurons. The close topographic location of GnRH-immunoreactive neurons and TH-immunoreactive nerve fibers was observed in the nucleus accumbens on days 17 and 20 and in the median eminence on day 20.

A quantitative radioimmunoassay for GnRH in the caudal regions of the GnRH neuron migration route in 21-day rat fetuses showed that injection of αMPT resulted in a drop of GnRH level in the anterior hypothalamus of female fetuses (Izvolskaia et al., 2009). This is additional evidence that catecholamines contribute to the regulation of development of GnRH neurons during prenatal ontogeny.

Probable mechanisms of the stimulating effect of catecholamines on the migration of differentiating GnRH neurons may involve regulation of the exchange of calcium ions, since the rate of their migration depends on the intracellular concentration of these ions. In mice, retardation of GnRH neuron migration at the cribriform plate of the ethmoid bone takes place against the background of sharp increase in intracellular calcium under the effect of tonic depolarization of GABAergic neurons (Bless et al., 2000). In the case of differentiating GnRH neurons, noradrenaline is apparently a signal molecule that reduces the level of GnRH secretion and probably causes cell membrane hyperpolarization. This neurotransmitter can serve as a functional antagonist of GABA and, acting upon previously depolarized GnRH neurons entering the brain through the cribriform plate, contribute to the maintenance of intracellular calcium level, thereby stimulating the migration of GnRH

neurons. It is also possible that catecholamines exert an indirect effect on the migration of these neurons by acting on their immediate cellular environment, in particular, on GABAergic neurons and cells synthesizing cell adhesion molecules. However, there is no evidence that GABAergic neurons migrating together with GnRH neurons are innervated by catecholaminergic nerve fibers and express catecholamine receptors. It is also less probable that the effect of catecholamines is mediated via regulation of the metabolism of cell adhesion molecules. Indeed, neither catecholamines themselves nor their antagonists (e.g., 6-hydroxydopamine) have influence on the synthesis of cell adhesion molecules in the nervous system of fetuses or adult animals (Messenger et al., 1999). On the other hand, some data indicate that noradrenaline partially inhibits the synthesis of β-tubulin, a cytoskeletal protein, which may results in the reduced rate of neuron migration (Messenger et al., 1999).
Sex-related differences in the distribution of GnRH neurons along their migration route manifest themselves only against the background of catecholamine deficiency.
Special attention has been recently devoted to the influence of cytokines on differentiation of GnRH neurons, but relevant published data are as yet scarce. One of such cytokines is HGF/SF, which has mitogenic, motogenic (stimulating cell motility), and chemoattractant properties with respect to nerve and other cells. HGF/SF appears in the nasal mesenchyme of embryos on day 12 of development, with its concentration increasing toward the brain and its c-Met receptor being expressed on GnRH neurons. The migration of GnRH neurons and the growth of their axonal cones become retarded if the HGF/SF concentration gradient is disturbed (Giacobini et al, 2007).
Another cytokine, LIF, exhibits a pleiotropic action during ontogeny, producing an effect on proliferation of primordial germ cells, differentiation of spermatocytes, blastocyst implantation, and the development of the pituitary and olfactory system . Experiments with the immature GnRH neuronal cell line GN11 have shown that LIF can induce hemokinesis of these cells. Both LIF and its receptor (LIFβ) are expressed in the nasal region of mouse embryos on day 13 of development, indicating a role for this cytokine in the migration of GnRH neurons.
The macrophage chemotactic protein-1 (MCP-1) is a powerful chemoattractant for many immune and nonimmune cells. Its main function is to guide the migration of leukocytes from hematopoietic organs to inflammation foci. As found recently, MCP-1 also stimulates migration of nervous stem cells in rats. Experiments with immortalized neuronal cell lines GT1-7 and GN11 and in vivo studies have shown that GnRH neurons themselves produce MCP-1 and express receptors for his factor, while MCP-1 has a stimulating effect on their migration in culture (Chattopadhyay et al, 2006).
The above facts suggest that the development of GnRH neurons and the hypothalamo–pituitary–gonadal system as a whole is apparently subject to dramatic changes upon activation of the mother's immune system during pregnancy. This assumption is confirmed by recent data on the effect of LPS on fetal brain development. It has been shown that LPS induces the synthesis of the vascular endothelial growth factor, nerve growth factor (NGF), antiapoptotic protein YB-1, neuronal differentiation factor (necdin), and BDNF in the fetal rat brain cortex (Liverman et al., 2006). On day 18 of embryonic development in mice, LPS suppresses the expression of factors involved in neuron migration and axonal cone growth, namely, of semaphorin 5b and chromatin-associated Groucho protein (Liverman et al., 2006). In addition, LPS increases the content of glial fibrillary acidic protein (GFAP), an intermediate filament protein, in hippocampal and cortical astrocytes and reduces the

content of myelin and immunoreactivity of the microglia in the offspring of LPS-injected rats during postnatal development. Intrauterine infection of LPS in rats results in an elevated level of GFAP in the brain white matter and hippocampus on postnatal day 7 and in the brain cortex and corpus callosum on postnatal day 14 (Yu et al., 2004). Chronic endotoxin-induced inflammation processes in the brain cause lesions in the white matter of pups examined on postnatal days 1 and 7, with these pups also showing a high level of GFAP expression on postnatal days 1 and 3 followed by active proliferation and differentiation of astrocytes (astrogliosis), on day 7 (Rousset et al., 2006).

Prenatal activation of the immune system by endotoxins modifies the stress response of the hypothalamo-pituitary system, the expression of proinflammatory cytokines in the brain, and the functioning of dopamin- and serotonergic systems (Wang et al., 2009). All these changes affect brain development, increasing the risk for neurological and mental disorders in remote periods. Induction of mother's immune response by LPS leads to changes in the levels of cytokines in different organs of the fetus. Proinflammatory cytokines are regarded as a connecting link between intrauterine infection during pregnancy and subsequent disturbances of brain functions in the fetus. Injection of LPS to pregnant mice induces increased expression of TNFα, IL-1β, and MCP-1 in fetuses (Liverman et al., 2006). In rats, the expression of TNFα is observed as early as 1 h after LPS injection and its level remaining unchanged for 24 h, while the level of IL-1β gradually decreases. The highest level of TNFα and IL-1β expression is observed during the first postnatal days. During intrauterine infection, cytokines TNFα и IL-1β appear to affect mainly the white matter of the fetal brain, which entails the development of cerebral palsy in newborn pups and characteristic symptoms of schizophrenia in remote periods (Yu et al., 2004).

Prenatal infection also affects the dopaminergic system of the fetus. In pregnant rats injected with LPS on day 11 of pregnancy, postnatal offspring are characterized by reduced numbers of dopaminergic neurons, increased activity of microglia, and a high level of proinflammatory cytokines, especially TNFα, in the substantia nigra. It is considered that, что LPS suppresses the secretion of glutathione (an antioxidant) in glial cells, which leads to the death of dopaminergic neurons and the development of Parkinson's disease. As shown recently, prenatal LPS infection in rats results in the attrition of dopaminergic neurons in the substantia nigra and serotoninergic neurons in the locus coeruleus, with consequent decrease in the contents of dopamine and serotonin in postnatal offspring (Wang et al., 2009). Such infection of pregnant rats can probably affect differentiation of monoaminergic neurons not only in the brain stem but also in other regions of the fetal brain, including the hypothalamus.

Initial data are also available on the effect of LPS on the GnRH system of newborn rat pups (Li et al., 2007). Stimulation of their immune system on the first postnatal days results in long-term sensitization of the GnRH system and its vulnerability to the inhibitory effect of stress in adult age. This effect is mediated by corticotropin-releasing hormone and its receptors in the median preoptic region.

According to our data, a single LPS injection to pregnant rats on day 12 of pregnancy suppresses the migration of GnRH neurons, whereas such an injection on day 15 has no effect on their distribution along the migration route (Fig. 3). After the injection on day 12 (but not on day 15), the total number of GnRH-immunoreactive neurons in the fetus was decreased on day 17 but returned to the normal (control) level by day 19. The effect observed on day 17 can be explained either by a general reduction of GnRH synthesis in these neurons or by a delay in the onset of their differentiation. In rats, GnRH neurons begin

to synthesize this hormone on day 15, i.e., one or two days after their formation, and the levels of LPS-induced cytokines in mother's blood and fetal tissues remain high only during 24 h after injection and then return to the baseline (Liverman et al., 2006). Therefore, the decrease in the numbers of fetal GnRH neurons observed on day 5 after LPS injection is unlikely to result from the direct influence of proinflammatory cytokines on GnRH synthesis in these cells. However, their indirect influence cannot be excluded, IL-1α and GM-CSF in adult animals block the release of GnRH from the axons of GnRH neurons by inhibiting the activity of NO synthase (Rettori et al., 1994). In view of these and our data, the most probable explanation is that LPS delays the onset of differentiation of GnRH neuron precursors. It should be noted that the total number of GnRH neurons returns to the norm by birth, but this does not exclude the occurrence of disturbances in the GnRH system functions during later periods of postnatal ontogeny.

Stimulation of the immune system in pregnant females by LPS on day 12 results to the suppression of not only differentiation but also migration of fetal GnRH neurons, which manifests itself in the increased numbers of these cells accumulating in the rostral brain regions, compared to the control (Fig. 1). On the other hand, LPS injection on day 15 does not lead to redistribution of GnRH-immunoreactive cells along their migration route by day 17 or 19. Thus, as GnRH cell differentiation is delayed, the start of migration of GnRH neurons shifts to later dates, and the rate of their intramesenchymal (intranasal) migration is retarded. On the other hand, LPS has no effect on the rate of their migration at later stages, when GnRH neurons pass through the cribriform plate of the ethmoid bone to the forebrain.

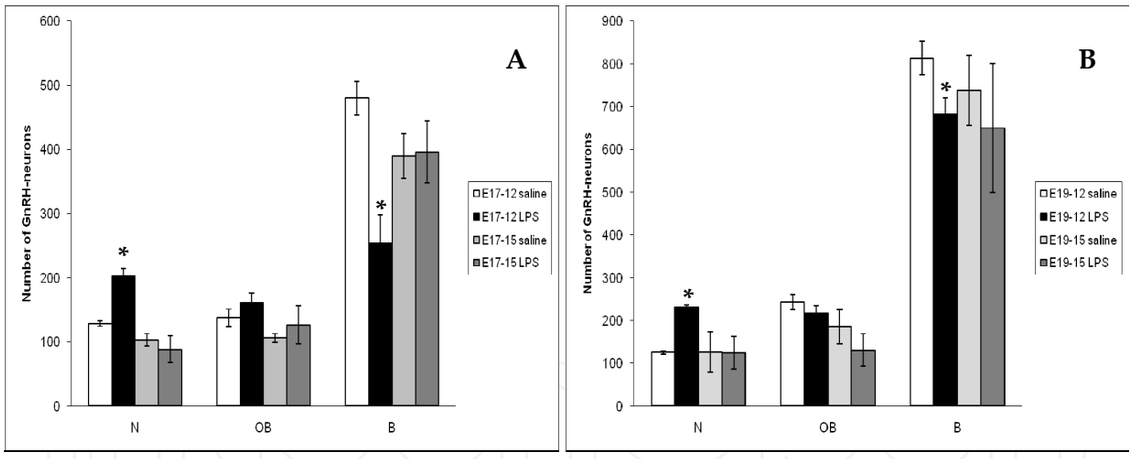

Fig. 1. Distribution of GnRH neurons in different areas of their migration in (A) 17-day and (B) 19-day rat fetuses injected with saline (control) or LPS on embryonic days (E) 12 and 15, $m \pm SD$ (E12: saline, n=6; LPS, n=6; E15: saline, n=3; LPS, n=3): N, nasal region; OB, olfactory bulbs; (B) brain. (*) Differences between the indicated values are significant at $p < 0.05$.

It is during the intramesenchymal migration that GnRH neurons express receptors for cytokines, primarily for IL-6 and LIF (Dozio et al., 2009), while their migration within the brain is apparently regulated by a different mechanism.

In the experiments described above, the migration of GnRH neurons within the nasal region appeared to be regulated via LPS-induced activation of the synthesis of proinflammatory cytokines. Therefore, we decided to analyze the effect of LPS at low doses (causing no more

than 25–30% fetal mortality) on the levels of cytokines IL-6, TNFα, LIF, and MCP-1 in pregnant mice and fetuses. Pregnant females were intraperitoneally injected with LPS (45 μg/kg body weight), and cytokines in the blood sera of females and fetuses and in fetal cerebrospinal and amniotic fluids were determined by means of flow cytometry and ELISA. The results showed that the blood levels of antiinflammatory cytokines in LPS-injected females were increased drastically, compared to the control: the increase was 38-fold for LIF, 28-fold for IL-6, 23-fold for MCP-1, and 20-fold for TNFα (Fig. 2). In fetuses, MCP-1 and IL-6 in tissues were increased by factors of two and seven, respectively, and LIF in the amniotic fluid was increased threefold. Thus, activation of the immune system by LPS in pregnant females has proved to result in elevated levels of proinflammatory cytokines in their peripheral blood and then in fetuses, with consequent disturbances in the migration and differentiation of GnRH neurons. The strongest effect on the migration of these neurons is apparently characteristic of IL-6, LIF and MCP-1.

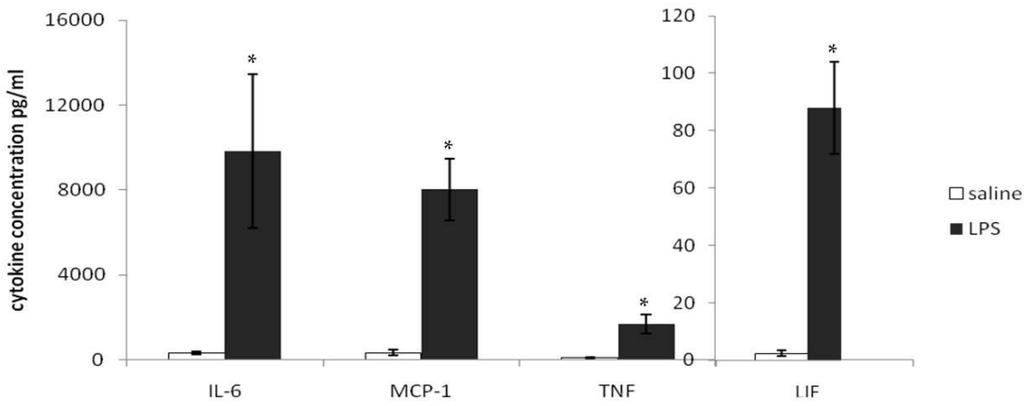

Fig. 2. Serum concentrations of proinflammatory cytokines in 12-day mouse fetuses 1.5 in 12-day mouse 1.5 hours after injection of saline (control) or LPS to the mother, $m \pm SD$ (saline, $n = 6$; LPS, $n = 5$). Abbreviations: IL-6, interleukin 6; LIF, leukemia inhibitory factor; MCP-1, macrophage chemotactic protein-1; TNF, tumor necrosis factor alpha. (*) Differences from the control are significant at $p < 0.05$.

2.3.3 Role of thymic peptides in reproductive system development and functioning

The thymus, being the primary organ of the immune system, can also be regarded as an endocrine organ. Moreover, it contains cells of neural origin that synthesize neuropeptides, which is evidence for its obvious relation to the nervous system. The thymus is the lymphoepitelian organ formed at the earliest stages of ontogeny. Its development begins on embryonic day 10 in rodents and embryonic week 4 in humans. Embryonic T-cell precursors migrate into thymus from the yolk sac, para-aortic splanchnopleura, and embryonic liver; in the postnatal period, the source of precursor cells is the bone marrow. Several systems of humoral regulatory factors operate in the thymus, including thymic peptides, hormones, neuropeptides, and cytokines. Their basic role is to provide for and regulate the development and functioning of T lymphocytes and thymic stroma and to control processes in the peripheral compartments of the immune and, probably, neuroendocrine systems (Goya et al, 2004).

A special place in thymus endocrinology belongs to thymic peptides, or hormones, which are relatively specific for this organ. These hormones, synthesized by epithelial cells of the thymus and released into the circulation, are distinguished into a separate group for the reason of their local synthesis (in the thymus) and sphere of action confined to the immune system. However, there is evidence for the synthesis of these peptides (except for thymulin) beyond the thymus and, in particular, in the nervous system (Hannappel et al., 2007). Thymic peptides appear to be cofactors in processes related to differentiation of thymocytes as well as to regulate the production of other hormones, neuropeptides, and cytokines in the thymus, hypothalamus, and pituitary. They are also involved in T-cell differentiation in the secondary lymphoid organs and in interactions with the hypothalamo–pituitary–adrenal and reproductive systems (Goya et al, 2004).

The thymus has a significant role in the functioning of the reproductive system (Fig.3). Thymic peptides, primarily α- and β-thymosins and thymulin, stimulate GnRH secretion in the mediobasal hypothalamus and gonadotropin secretion in the pituitary of female rats (Garcia et al., 2005). In male rats, prepubertal thymectomy is followed after 45 days by a drop of FSH and a rise of luteinizing hormone and testosterone levels in the peripheral blood.

In perinatal ontogeny, the thymus is indispensable for the formation of the pituitary-gonadal axis. Prenatal thymectomy in primates and neonatal thymectomy in rats or mice result in suppressed oogenesis, reduced weights of the ovaries and adrenals, and decreased levels of gonadotropins in the pituitary and circulating blood during postnatal life (Farookhi, 1988). Disturbances in the immune system manifest themselves 25–30 days after thymectomy. In particular, thymectomy on postnatal day 3 leads to the paucity of regulatory T cells, loss of peripheral tolerance, and development of organ-specific autoimmune disease in adult mice. Moreover, it induces production of auto-oocyte antibodies detectable in the circulation, with consequent development of autoimmune ovarian dysgenesis. Importantly, day 3 thymectomy does not necessarily lead to autoimmune disease in all mouse strains, indicating that processes responsible for the disease development are genetically controlled (Roper et al., 2002).

Neonatal thymectomy also affects the male reproductive system, but its consequences manifest themselves relatively late. A drop in the levels of luteinizing hormone and prolactin takes place on days 60–90 after thymectomy, and symptoms observed on days 13-170 include testicular atrophy, hypertrophy of pituitary β-cells, and lymphoid infiltration of the pituitary, thyroid, and prostate (Farookhi, 1988). It should be noted that thymectomy on postnatal day 10 also results in retarded sexual development (with reduced numbers of follicles, low levels of blood estrogens, etc.), as does neonatal thymectomy. Thymulin corrects these disturbances, while in normal mice it has no effect on estrogen secretion (Goya et al, 2004; García et al., 2005).

In mutant nude (athymic) mice, disturbances are observed not only in the immune system but also in the neuroendocrine and reproductive systems. Embryonic development of the thymus in these mice is controlled by gene *Foxn1* located on chromosome 11. It proceeds normally until embryonic day 11, when the complex architecture of the thymus becomes distorted, which interferes with differentiation of thymic epithelial cells and colonization of the organ by lymphoid precursor cells. Changes in the reproductive system of athymic mutants are similar to those in neonatally thymectomized mice.

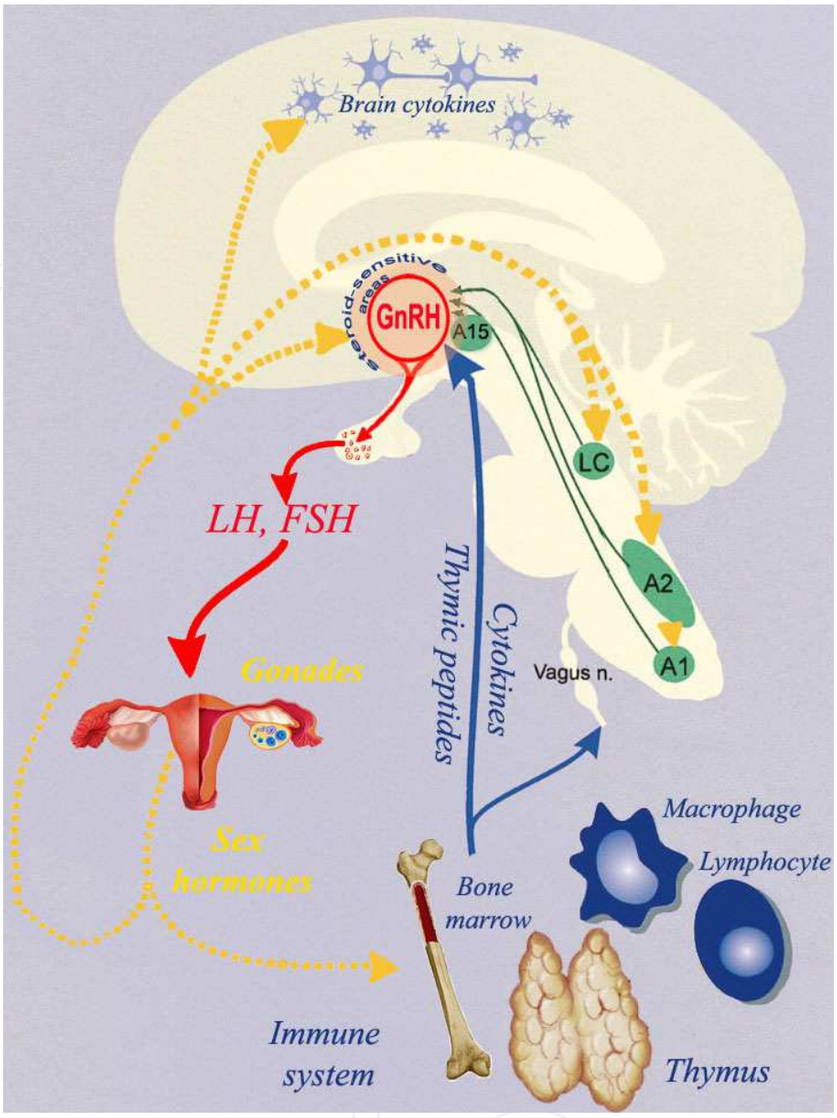

Fig. 3. Interactions of the GnRH system with the hypothalamo–pituitary–gonadal axis and immune system. Abbreviations: GnRH, gonadotropin releasing hormone-producing neurons; LH, luteinizing hormone; FSH, follicle stimulating hormone; LC, locus coeruleus; A1, A2, and A15, catecholamine-producing (tyrosine hydroxylase-immunoreactive) cell groups in the brain.

Acidophilic and basophilic pituitary cells in the mutants are smaller than normal, and the synthesis of the growth hormone, prolactin, FSH, and luteinizing hormone is reduced (Goya et al, 2004). Thymic peptides, thymulin in particular, correct these disturbances (García et al., 2005). Neonatal thymulin gene therapy in nude mice results in normalization of blood thymulin and gonadotropin levels at maturity (Goya et al., 2007). Thus, the hormonal hypofunction of the thymus during early ontogeny entails long-term or irreversible disturbances in the structure and functions of both immune and reproductive systems.
The sum of available data suggests the following scheme of interactions between the hypothalamo-pituitary reproductive system and the thymus (Fig. 3). Hypothalamic GnRH

interacts with specific receptors on epithelial cells of the thymus, thereby inducing the synthesis of thymic peptides by these cells and differentiation of T lymphocytes, the latter process involving participation of thymic GnRH and sex hormones. Thymic peptides, in turn, stimulate the secretion and functional activity of hypothalamic GnRH, which induces the secretion of gonadotropins and thereby modulates steroidogenesis.

3. Conclusion

The data considered in this review demonstrate that interactions of the hypothalamo–pituitary–gonadal and immune systems are a lifelong phenomenon that begins during embryonic development. The pattern of establishment and development of their interactions during early ontogeny is a major factor in programming the health of an individual. Changes in these systems upon perinatal exposure to various adverse factors upset the normal homeostatic balance of the body, causing disturbances in their functioning throughout the subsequent life span. The plasticity of physiological systems during early ontogeny provides for effective adaptation of the developing organism to variable ambient conditions; on the other hand, it is responsible for long-term or even permanent alteration of general response to environmental factors. Thus, thymic peptide deficiency in neonatally thymectomized or nude mice or increased levels of proinflammatory cytokines resulting from bacterial infection in a pregnant female cause disturbances in the formation of various brain systems, thereby affecting differentiation of GnRH neurons and, therefore, the establishment of the reproductive function. Since high concentrations of sex steroids can significantly intrude on the formation of the neuroendocrine–immune axis, caution should be taken in prescribing sex steroids and their synthetic analogs. In particular, this concerns prenatal treatment with estriol recommended by some specialists. Special attention should also be given to the children whose mothers suffered an infectious disease during pregnancy. On the other hand, experimental and clinical data accumulated to date provide evidence for a favorable effect of estrogens on patients with autoimmune diseases, e.g., multiple sclerosis.

The patterning of sexual behavior of sex steroids takes place not only during early development: these hormones can alter the prenatal programming of relevant systems at later stages of ontogeny, with adolescence being most responsive to their influence. The effects of GnRH and sex hormones on the immune system during adult life are apparently nonspecific and serve to maintain its homeostasis in response to changes in ambient conditions or to stress-induced immunosuppression. Indeed, thymocyte deficiency resulting from age-related thymus involution or stress can be reversed by treatment with hormones, including GnRH and its agonists.

4. Acknowledgments

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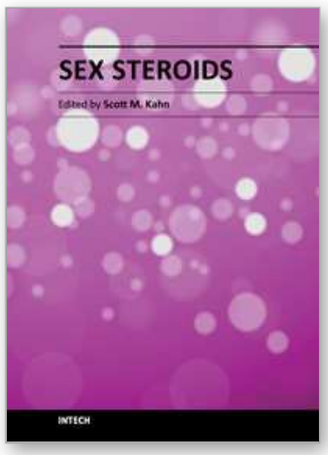

Sex Steroids

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