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AMYGDALOHIPPOCAMPAL AREA IN ADULT MALE RATS AFTER PROGESTERONE TREATMENT

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Neurons of amygdalohippocampal area (AHA) of the amygdaloid complex (AC) in adult control and progesterone (P) neonatally treated adult male rats were studied using light microscopy and morphometric analysis. Progesterone in a single dose of 1.25 mg was administered at the age of 5 days (neonatal period) and in a dose of 5 mg at 30 days of age. Two stereological parameters were estimated: the volume density (V_v) (mm^o) AHA cell nuclei, cytoplasm, neuropil and the numerical density (N_v) (mm^{-3}) of neurons. In adult, neonatally and juvenilely treated male rats (V_v) (mm^o) AHA cell nuclei, cytoplasm and numerical density (N_v) (mm^{-3}) of neurons were significantly higher ($p<0.05$ and $p<0.001$) while V_v of neuropil was significantly lower ($p<0.001$) compared with the values of investigated parameters in the controls.

Key words: amygdaloid complex, amygdalohippocampal area, progesterone, rats, stereology

INTRODUCTION

Throughout the life span, the brain continues to be shaped and modified by the external world acting through the release and actions of circulating hormones and endogenous growth factors and neurotransmitters (McEwen, 2001). Gonadal steroid hormones are involved in the organization of neural circuits of the developing rat brain with the most dramatic structural changes in the central nervous system occurring during gestation and early postnatal period of life (Arnold and Breedlove, 1985; Arnold and Jordan, 1988; Pilgrim and Hutchinson, 1994; Gorsky, 2000; Merke *et al*., 2003). They influence the activity and plasticity of neurons and glial cells during early development and they continue to exert trophic and protective effects in the adult nervous sistem. Steroids, including progesterone (P) produced by gonads and adrenal glands reach the brain, spinal cord and peripheral nerves via the blood stream (Schumacher *et al*., 2000).

Sex steroid hormones have organizational and activational effects on the sex steriod-accumulating neuronal structures in the central nervous system such as hypothalamic nuclei and nuclei of the amygdaloid complex (AC) (Matsumoto,

1991; Gomes and Newman,1991; Wood and Coolen, 1997). In the brain regions which have target neurons for sex steroids, neuronal migration, cell death, differentiation of cell types and inhibition or expression of some of neuropeptides involved in the regulation of reproductive functions, are processes that could be modulated by hormones and result in sex differences in neural development (Arnold and Gorsky, 1984; Mycevich *et al.*, 1994; Bradley *et al.*, 1999; Mc Ewen, 2001). The organizational effect of sex steroid hormones also implies permanent influences on a variety of morphological characteristics such as neuronal size, neuron number, dendritic branching, spine density and the synaptic connectivity within different brain areas and different species (Matsumoto, 1991; Gould *et al.,* 1991; Wooly and Mc Ewen, 1993; McEwen *et al.,* 1999). New investigations showed that gonadal steroid hormones play an important role in the proliferation, survival, activation and neuroprotection of neurons. In such a way, Flower *et al*. (2003) showed that newly prolifereted cells in the adult male amygdala were affected by gonadal steroid hormones respectively, that gonadal steroid hormones influenced the number of newly proliferated cells in the amygdala. There are newly discovered ways in which gonadal steroid hormones (estrogenic compaunds) protect nerve cells from damage, free radicals and neurodegeneration (Lee and McEwen, 2001).

In this work, we investigated the amygdalohippocampal area (AHA), the most caudal part of the sexually dimorphic MN of AC, which poses gonadal steroid receptors (Simerly, 1993, De Vries and Simerly, 2002) and it is very important for the neural control of reproductive behavior (Nishizuka et Arai, 1981; Mizukama *et al.,* 1983; Gomez and Newman, 1992; Wood and Coolen, 1997). This posterior area of MN including AHA belongs to the medial sexually dimorphic area (SDA) (De Vries *et al.,* 1988, De Vries and Simerly, 2002) and is part of an interconnected vomeronasal pathway and telencephalo - hypothalamic circuit the development of which is influenced by gonadal hormones during early postnatal period (Mycevich *et al*., 1994; De Vries and Simerly, 2002). Our attention was focused on the long term effects of a single dose of P administered to neonatal and juvenile male rats which were sacrificed in the adult period.

MATERIAL AND METHODS

To investigate the influence of P on the morphology of the AHA in adult rat brain after postnatal P tretatment, we used two groups of 10 male Wistar rats. The animals were treated: on 5th day of life (neonatal period) with 1.25 mg P and on the 30th day of life (juvenile period) with 5 mg P. As controls served 10 non-treated age-matched male rats. The animals were sacrificed on the 62 nd day of life, in the adult period, under ether narcosis. The brains were removed immediately and AC with surrounding structures including anterior hippocampal area were isolated and fixed in Bouin solution. After standard paraffin embedding, serial sections (5 μm thick) were stained with hematoxylin-eosin and Herlant methods. Stereological analysis was done by light microscopy (magnification -1088 x).

For stereological analyses, two morphological parameters, the volume density (V_v) (mm^o) of AHA neuronal nuclei, cytoplasm, neuropil and numerical density (N_v) (mm^{-3}) of neurons were estimated, using the Weibel multipurpose test sistem (P:42). Sampling was performed so that the most caudal sections in the area of MN were used and 50 test fields were chosen by the intermittent sampling (Kališnik, 1985). The statistical significance was tested with Student's t-test for levels of significance $p<0.05$, $p<0.01$ and $p<0.001$.

RESULTS AND DISCUSSION

In the adult rat, the amygdalohippocampal area appears immediately caudal to the main body of medial nucleus (MN) and ventral to posterodorsal part of the same nuclei. It consists of well stained, tightly-packed cells, very similar to neurons in the posterior part od MN. On its lateral side this neuronal structure merges with the basomedial nucleus and the ventral part of the lateral entorhinal area. Caudally, AHA is continuous to the hippocampal formation.

The results of stereological analysis of AHA in treated and control male rats are summarized in Tables 1, 2 and 3. Values of investigated stereological parameters i.e. volume density (V_v) in control male rats was: 0.052 (mm^o) or 5.2 % for neuronal nuclei, 0.037 (mm^o) or 3.7% for cytoplasm and 0.9104 (mm^o) or 91.04 % for neuropil (Table 1). In neonatally treated adult animals this parameter was: 0.072 (mm^o) or 7.2 % for neuronal nuclei, 0.053 (mm^o) or 5.3% for cytoplasm and 0.8742 (mm^o) or 87.42% for neuropil (Table 2). In juvenilely treated adult male rats volume density for neuronal nuclei was 0.064 (mm^o) or 6.4 %, for cytoplasm 0.0619 (mm^o) or 6.19 % and for neuropil 0.8780 (mm^o) or 87.80% (Table 3). Numerical densities (N_v) of AHA neurons were: 10.55×10^4 (mm^{-3}) in controls, 17.01×10^4 (mm^{-3}) in neonatally treated and 14.05×10^4 (mm^{-3}) in juvenilely treated adult male rats. These results demonstrated that in neonatally and juvenilely treated adult male rats (V_v) (mm^o) of AHA cell nuclei and of cytoplasm were significantly higher ($p<0.05$) than in controls, while those of neuropil were significantly lower ($p<0.001$) than in controls. The numerical densites (N_v) (mm^{-3}) of neurons in neonatally and juvenilely treated adult male rats were also significantly higher ($p<0.001$).

Table 1. Investigated stereological parameters of AHA in control male rats

Controls	Σx	$\bar{x}$	$\pm$SD	V_v (mm^o)	V_v (%)	N_v (mm^{-3})
Nucleus	110	2.20	1.01	0.052	5.2	
Cytoplasm	78	1.56	1.21	0.037	3.7	
Neuropil	1912	38.24	1.01	0.9104	91.04	
Nº of neurons	2924	58.48	4.05			10.55×10^4

Table 2. Investigated stereological parameters of AHA in neonatally treated adult male rats

Neonatally treated	Σx	$\bar{x}$	$\pm$SD	V_v (mm^o)	V_v (%)	N_v (mm^{-3})
Nucleus	152	3.04	1.18	*0.072	*7.2	
Cytoplasm	96	1.92	1.11	*0.053	*5.33	
Neuropil	1836	36.72	1.71	***0.8742	***87.42	
N^o of neurons	4378	87.56	3.50			***$17.01x10^4$

Table 3. Investigated stereological parameters of AHA in juvenilely treated adult male rats

Juvenilly treated	Σx	$\bar{x}$	$\pm$SD	V_v (mm^o)	V_v (%)	N_v (mm^{-3})
Nucleus	136	2.72	1.17	*0.0640	*6.40	
Cytoplasm	67	1.34	0.90	*0.0619	* 6.19	
Neuropil	1916	38.31	1.39	***0.8780	***87.80	
N^o of neurons	3614	72.28	3.85			***$14.05x10^4$

Σx - total number of intersections; $\bar{x}$ - mean value;
SD - standard deviation; V_v - volume density; N_v - numerical density.
*-$p<0.05$ **-$p<0.01$ ***-$p<0.001$

In the present report we investigated the influence of P on AHA as part of posterior AC in adult rats brain which were treated during postnatal period of life (in the neonatal and in the juvenile period). Perinatal development is often viewed as the major period of time for organizing of steroid – sensitive neural circuits by steroid hormones. Behavioral and neuroendocrine responses to steriods are dramatically different before and after puberty, suggesting that puberty is another period of time during which gonadal steroids affect neural development (Romeo *et al.,* 2000). Peripheral steroid hormones act on brain tissues through intracellular receptor-mediated mechanisms to regulate several important brain neuronal functions (Schumacher *et al.,* 2000). Most hormonal actions in the brain are mediated by their cognitive nuclear receptors which were ligand-regulated transcription factors (Tsai and OMalley, 1994). In different brain areas with sex steroid accumulating neuronal structures (such as AC), sex steroids promote neuronal and glial differentiation (Mong *et al.,* 1999) and induce permanent sexual dimorphism: in nuclear volume (Gorsky *et al.,* 1978), neuronal number (Guillamon *et al.,* 1998; Lozanče *et al.,* 1994;1995), distribution patterns of serotenergic and vasopressinergic fibers (Simerly *et al.,* 1982; De Vries *et al.,* 1983), synaptic formation and neuronal connectivity (Nishizuka and Arai, 1981; Sakuma and Pfaff, 1981) and in soma size of neurons (Bradley *et al.,* 1999). The effects od steroids in

the modulatory role of the AC may be expressed via the involment of steroid sensitive neurons and the presence of highly specific steroid receptors (Yokosuka *et al.,* 1997; Nishikara *et al.,* 2003) or via rapid regulatory effects on several membrane-associated and intracellular responses that do not depend on changes in gene expression (nongenomic mechanisms) (Beyer and Karolczak, 2000; McEwen 2001). These include changes in the electrical properties of neurons, as well as alterations in neurotransmitter release (Navarro *et al.,* 2003). Some steroid hormones, named "neurosteroids" can also be synthesized within the nervous system. They include prognenolone, P and their reduced metabolites and sulfate esters (Akawa and Baulieu, 1999; Schumacher *et al.,* 2000; Mayo *et al.,* 2001; Semeniuk *et al.,* 2001).

Generally, present stereological analysis showed that treatment with P in neonatal and juvenile (late puberty) periods of life caused effects on AHA in male rats. That is demonstrated by the values of investigated morphometric parameters in adult rats.The value of N_v in neonatally and juvenilely treated male rats showed a significant increase in the number of neurons and in volume density of AHA neuronal nuclei and cytoplasm (in regard to values in control male rats). Beyer and Feder (1987) described that perinatal gonadal steroids produced observable changes in behavior and physiology that were not concurrent with the first administration of the hormone but manifested themselves several weeks or months after a second application of the hormonal stimulus. In the brain, most hormonal actions are mediated by their cognate nuclear receptors which are ligand-regulated transcription factors (Tsai and OMalley, 1994). Đelić *et al*. (2003) in adult male rats brain, after neonatal P treatment, observed the long term effects on the number of neurons in different nuclei of AC, as well as in other brain nuclei. Perinatal steroids probably produced immediate cellular changes that were not manifested until much later, when appropriate hormonal conditions were present (production of adequate amounts for sex steroids beginning puberty). Siburg et al. (1991) suggested that the plasticity of sex steroids receptor system in the rodent brain is not only dependent on development, but also on hormonal status of the animals. In the moment of sacrifice, the animals in our experiment were in the adult period when adeequate hormonal conditions have been present, as well as in juvenile treated animals. Possible genomic effects, consisted of a shortening of latency and an enhancement of the response to a second administration of the hormone. At the cellular level, this change in responsiveness is apparently related to a persistent change in chromatine structure that allows the receptor-hormone complex to interact more efficiently with specific sites on the DNA (Burch and Wientraub, 1983). Progesterone presumably binds to the receptor complex which than stimulates the protein synthesis mechanism of the cell. Increases in specific cytoplasmic organelles including rough endoplasmic reticulum, polyribosomes and proliferation of Golgi apparatus after treatment with sex steroid hormones, suggest a stimulation of protein synthetic capacity of the cell (Carrer and Aoki, 1982; Meisel and Pfaff, 1985). It has been shown that P as "neurosteroid" plays an important role in the formation of new myelin sheath and that it promotes myelinisation by activating the gene expression of genes coding myelin proteins (Schumacher *et al.,* 2000). Progesterone, as a neurosteroid in Purkinje neurons

only during neonatal life, may be involved in the promotion of neuronal and glial growth and neuronal synaptic contact in the cerebellum (Tsutsui *et al.,* 2000). Rupprecht (1997) demonstrated that some of steroid hormones including derivates of P as neuroactive steroids can regulate also gene expression via the P receptor after intracellular oxidation. He described that in physiological concentrations these neuroactive steroids regulated the neuronal function through their concurrent influence on transmitter-gated ion channels and gene expression. Neurons of AHA of AC through receptors and genomic expression may also be stimulated to increase a production of cytoskeleton elements or membranous components that contribute to the maintanance of their structure. However, as in our earlier studies, we have not ruled out the possibility that the observed changes in AHA are secondary steroid-mediated changes provoked elsewere in the brain, which in turn may result in altered inputs to neuronal structures of AC.

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AMIGDALO-HIPOKAMPALNA ZONA ODRASLIH MUŽJAKA PACOVA TRETIRANIH PROGESTERONOM

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SADRŽAJ

Morfometrijskom analizom uz pomoć svetlosne mikroskopije ispitivani su neuroni amigdalo-hipokampalne zone (AHA) amigdaloidnog kompleksa (AK) odraslih mužjaka pacova - kontrola i odraslih mužjaka pacova tretiranih progesteronom. Progesteron je aplikovan u dozama od 1,25 mg 5. dana (u neonatalnom periodu) i 5 mg - 30. dana (u kasnom juvenilnom) periodu života. Praćena su dva stereološka parametra, zapreminska gustina (V_v) (mm^o) jedra neurona, citoplazme i međućelijskog prostora, i numerička gustina neurona (N_v) (mm^{-3}). U neonatalno i juvenilno tretiranih mužjaka pacova volumenska gustina (V_v) (mm^o) AHA jedara neurona i citoplazme i numerička gustina (N_v) (mm^{-3}) neurona odraslih mužjaka pacova bile su značajno povećane ($p<0,05$ i $p<0,001$), dok je V_v neuropila bila značajno niža ($p<0,001$) u poređenju sa vrednostima ispitivanih parametara kod kontrolnih životinja.