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LOCALIZATION OF MONOAMINE POSITIVE STRUCTURES IN THE OVARY AND OVIDUCT OF DEVELOPING RATS

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The aim of this study was to investigate the localization and distribution of sympathetic positive structures in the female gonads and oviducts of 15, 30 and 60-day-old AO rats. Histofluorescence and immunohistochemistry methods were used to determine their distribution in the ovary and oviduct, as well as for identification of dopamine and serotonin within sympathetic positive structures. Total monoamine positive structures (fibers and cells) were mainly localized under the surface epithelium, between follicles, especially surrounding groups of primary follicles and between secondary interstitial cells. The distribution of dopamine (DA) immunolabelled fibers and cells was in accordance with the distribution of total monoaminergic structures detected using histofluorescence. However, the density of structures labeled with DA antibodies was lower compared to total catecholamine positive structures detected by the fluorescence method. Delicate serotonin (5-HT) positive fibers were present mainly under the surface epithelium and in interstitial tissue between the cortex and medulla. In the hilum and medulla 5-HT positive cells were found perivascularly, while a dense population of 5-HT positive cells was found in the oviduct and mesovarium in 60-day-old animals. No corpus luteum cells were labelled using either of the two methods. Our findings corroborate observations that the monoamine supply of the ovary is not exclusively via extrinsic innervation and that intragonadal sources have an important role in their synthesis. Furthermore, the intraovarian localization of these elements suggests that monoamines exert direct or indirect effects on ovarian function.

Key words: ovary, monoamines, DA, 5-HT

INTRODUCTION

The role of the hypothalamo-pituitary axis in regulation of ovarian function(s) is well documented (for review see Freeman, 1994). However, accumulation of new data strongly implies a complementary role of local functionally diverse

factors, which are produced within the ovary. These include growth factors, cytokines, prostaglandins and neurotransmitters (Adashi, 1992; Hafez, 1993). Neurotransmitters have been the subject of recent studies because of their wide distribution in the central and peripheral nervous systems, which mean that they must be present in the reproductive system at least as a result of release from nerve terminals in the ovary and adnexa.

The ovary is innervated by sympathetic, parasympathetic and sensory fibers of the peripheral nervous system. Sympathetic innervation to the rat ovary reaches the organ by two separate routes: via the ovarian plexus and through the superior ovarian nerve in the suspensory ligament. The majority of ovarian sympathetic nerve profiles are derived from the nerve in the suspensory ligament, which innervates both blood vessels and interstitial tissue, while those derived from the ovarian plexus terminate perivascularly (Lawrence and Burden, 1980). The relative abundance of each of these nerve fibers may be different among mammalian species (Burden, 1985). The nerve fibers are in close vicinity to different cells in the ovary, which implies release of neurotransmitters into the interstitial space close to neighboring target cells, bearing receptors (Mayerhofer *et al.*, 1999).

Besides extrinsic innervation of the ovary, many authors attribute the release of neurotransmitters to different local sources. Some of them are released by either mast cells or some blood elements (Amenta *et al.*, 1992; Finocchiaro *et al.*, 1994), or may be derived from intrinsic sources, including neurons, neurone-like cells or even typical ovarian cells (Mayerhofer *et al.*, 1999; D'Albora *et. al.*, 2000).

Considering the previously mentioned data, the aim of our investigation was to describe the distribution of monoamine positive structural elements (norepinephrine, dopamine and serotonin) in rat ovaries and oviducts during the juvenile and pubertal period. The distribution of total monoamines was investigated using a fluorescence method while DA and 5-HT positive structures were identified using immunohistochemistry.

MATERIAL AND METHODS

Animals and general procedure:

Female inbred AO rats were used in these experiments. They were kept in our animal colony under standard laboratory conditions with free access to food and water. The animals were sacrificed by rapid decapitation on the 15^{th} and 30^{th} day of life and on the day of the first estrous after 60 days of postnatal life. Vaginal smears stained with haematoxylin and eosin were examined to determine the stage of estrous cycle. Ovaries and oviducts were removed carefully, in aseptic conditions, snap frozen and stored at -70°C until sectioning. Sequential serial sections of ovaries and oviducts, 5-20 μm thick, were obtained, using a Reichert cryocut at -20°C, and mounted on clean slides. Consecutive ovary and oviduct sections were treated by fluorescence histochemistry and immunocytochemical methods. At least 5 ovaries and oviducts were used for each time point.

Fluorescence histochemistry:

Monoaminergic innervations of the ovaries and oviducts were examined using the glyoxylic-acid-induced histofluorescence (de la Torre, 1980). The slides were immediately dipped into a solution containing 2% glyoxylic acid, 0.2 M sucrose and 0.236 M monobasic potassium phosphate (pH 7.4) for ten minutes and dried under a gentle warm airflow. We standardized the time between cryocut sectioning and dipping in glyoxylic acid and used two hair dryers with standardized drying time and temperature to assure comparable fluorescence. The sections were then covered with immersion oil, heated at 95°C for 2.5 minutes and immediately coverslipped. All sections were analyzed on the same day to prevent diffusion decomposition of fluorescence.

Immunohistochemical staining:

Five-micrometer thick cryocut sections were fixed first in cacodylate and sodium metabisulfite (pH 6.2) solution, after that in a solution of cacodylate, sodium metabisulfite and glutaraldehyde (pH 7.5) for 15 - 30 minutes. Tris metabisulfite solution (pH 7.5) was used for washing the slides. To reduce non-specific staining all sections were preincubated in a solution of Tris metabisulfite with sodium borohydride (pH 7.5). They were rinsed 4 times with Tris metabisulfite solution and incubated with specific rabbit primary antibody overnight at 4°C in a humid chamber. After three washings with Tris metabisulfite solution, the sections were incubated with goat antirabbit antibody for 1 hour at 37 °C. Thereafter, the sections were washed in three changes of Tris metabisulfite solution and incubated with peroxidase anti-peroxidase complex for 1 hour at 37°C. Peroxidase activity was detected by treating sections with 3'3-diaminobenzidine in 0.05M Tris with 0.02% H_2O_2 and mounting them in gelatin/glycerol medium of. At least one section was processed as a control in the way that the staining procedur was performed with one component omitted each time.

All sections were examined and photographed under an Olympus BH2 photomicroscope. For fluorescence histochemistry sections were examined under the same photomicroscope with exciting filter BP - 405 and barrier filter Y - 475.

Antisera and Conjugates:

Primary antibodies were provided by NEOSYSTEM, France. DA antiserum was used for labeling dopaminergic positive structures in the ovary and oviduct, while for identification of serotoninergic positive profiles 5-HT antiserum was used. Both antisera were diluted 1:2000. Final dilutions were made in a solution of Tris metabisulfite with Triton X-110 and non-specific serum. Goat anti-rabbit antiserum diluted 1:100 (Tris metabisulfite solution) was used as the secondary antibody. The peroxidase anti-peroxidase complex was purchased from Sigma Chemical Company.

RESULTS

Total monoaminergic structures

Using fluorescence histochemistry monoamine positive structures were visualized in all studied groups but with different localization and intensity of fluorescence during the investigated period. In the ovaries scarce and subtle fibers were found underlying the surface epithelium, in interfollicular tissue and

around blood vessels. Moreover, a fine granular fluorescence was observed near the primary follicles, and even in some follicles between follicular cells in 15-day-old females (Fig. 1). Beside this localization, in 30 - and 60 - day - old females, bundles of nerve fibers and a few fluorescing cells were present in the cortex between follicles (Fig. 2A), and intensive fluorescence was noticed

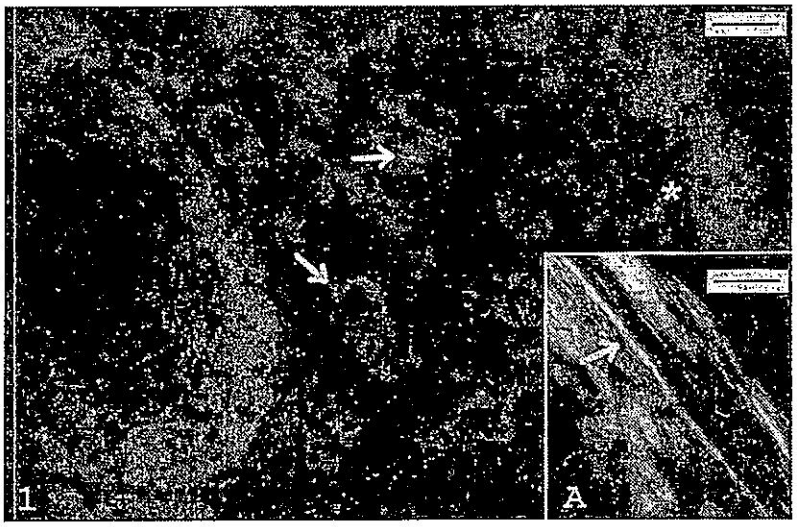

Figure 1. Fluorescent nerve profiles localized near to the primary follicles (→) and between follicular cells (*) in the ovary in a 30-day-old-rat. (Bar=21μm)
Insert A - Fibers underlying the surface epithelium (→) (Bar=21μm)

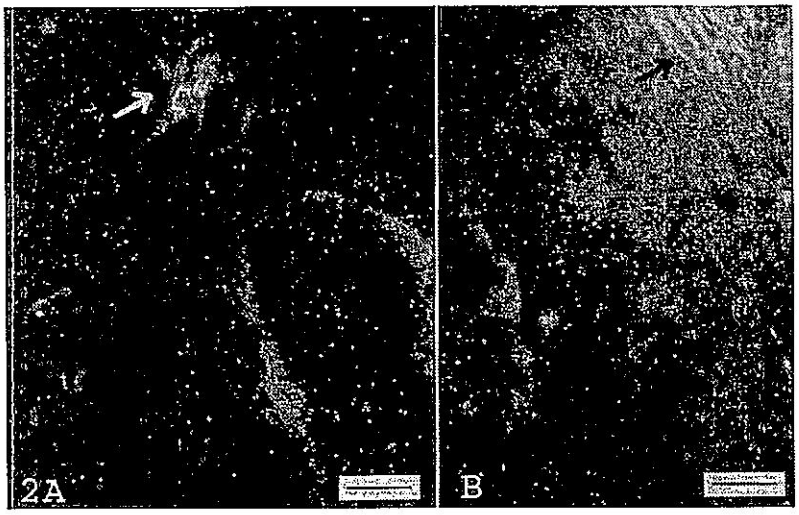

Figure 2. (A) Fluorescent nerve fibers (→) present in the interfollicular ovarian tissue in 30-day-old rats (Bar=84μm) and (B) positive nerve fibers (→) and cells (*) in the lamina propria mucosae and oviductal tela subserosae in a 60-day-old-rat. (Bar=21μm)

between secondary interstitial cells too. At these ages fine varicose profiles and cells in the mesovarium and in the lamina propria mucosae and tela subserosae of the oviduct were observed (Fig. 2B).

Dopamine and serotonin positive structures

In the ovaries of all ages, fine varicose networks of DA-positive fibers were found around small primary follicles (Fig. 3A), between secondary interstitial cells and in interfollicular tissue (Fig. 3B). In 15-day-old females weakly stained fibers were found beneath the surface epithelium. In addition, in the cortex of 30- and 60-day-old animals bundles of DA-positive fibers extended between the tunica

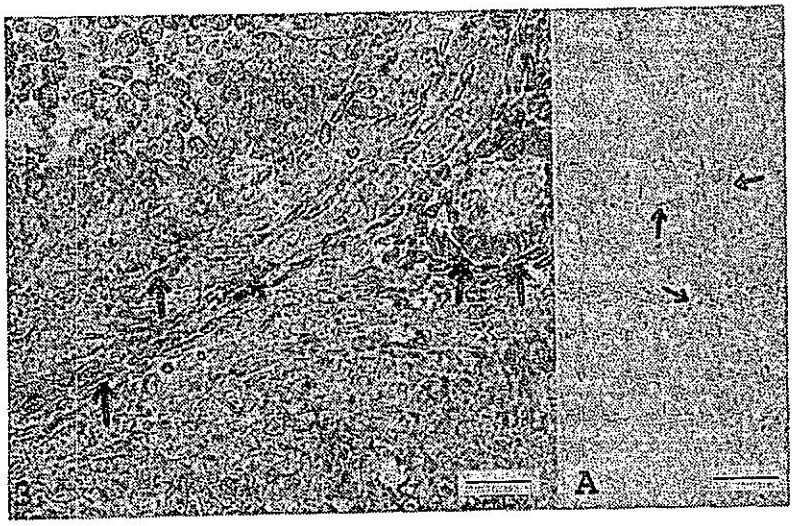

Fig. 3. Fine DA-positive fibers around a small primary follicle and in interfollicular tissue (→), and a DA-positive cell (*) in 30-day-old rat. (A) DA-positive fibers between secondary interstitial cells in a 60-day-old rat (→) (Bar=21μm)

albuginea and the medulla. A few DA positive cells were localized in interfollicular tissue (Fig.4A). Dopamine positive fibers were sparsely distributed through the mesovarium (Fig. 4B) and in tela subserosa of the oviduct.

Immunohistochemical staining with 5-HT antibodies revealed the presence of sparsely positive fibers within the ovaries of 15- and 30-day-old rats. These fibers were localized mainly under the surface epithelium (Fig. 5A) and in interstitial tissue between the cortex and medulla (Fig. 5B). Furthermore, a dense population of small 5-HT positive cells was present in the mesovarium (Fig.6A) and in oviductal tela subserosa in the ovaries of 60-day-old females (Fig. 6B).

The analysis of corpora lutea in 60-day-old females revealed that no luteal structures were labeled using either of the two methods.

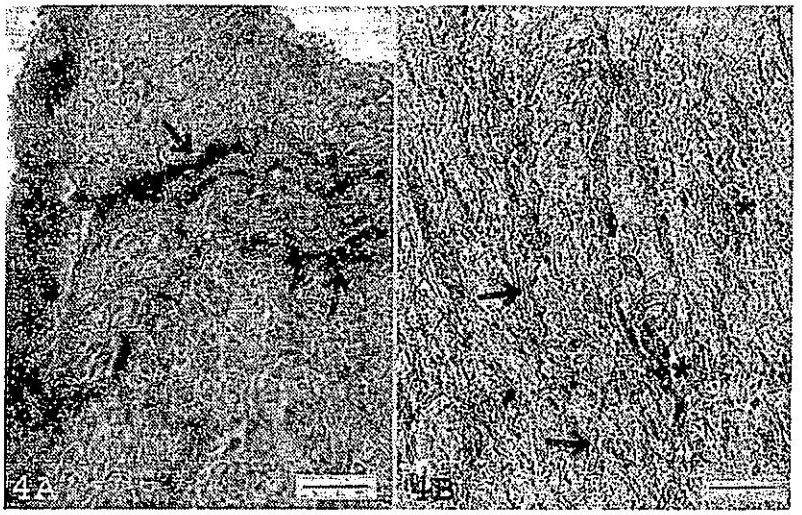

Fig. 4. (A) Bundles of DA-positive fibers extend from the tunica albuginea towards the medulla (→). (B) Dopamine-positive fibers (→) and cells (*) localized in the mesovarium in a 60-day-old-rat. (Bar=21μm)

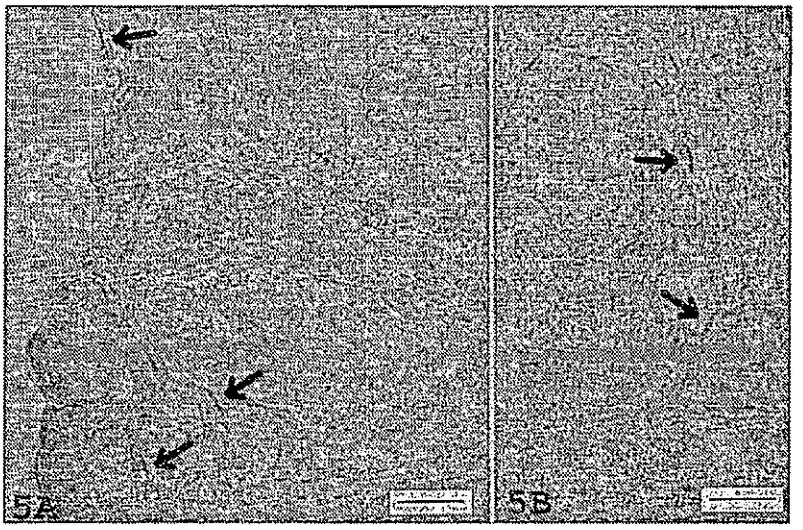

Fig. 5. (A) 5-HT positive fibers sparsely localized under the surface of the epithelium and between follicular cells in a 30-day-old-rat (→). (B) 5-HT positive fibers in the interstitial tissue between the cortex and medulla in a 15-day-old rat (→). (Bar=21μm)

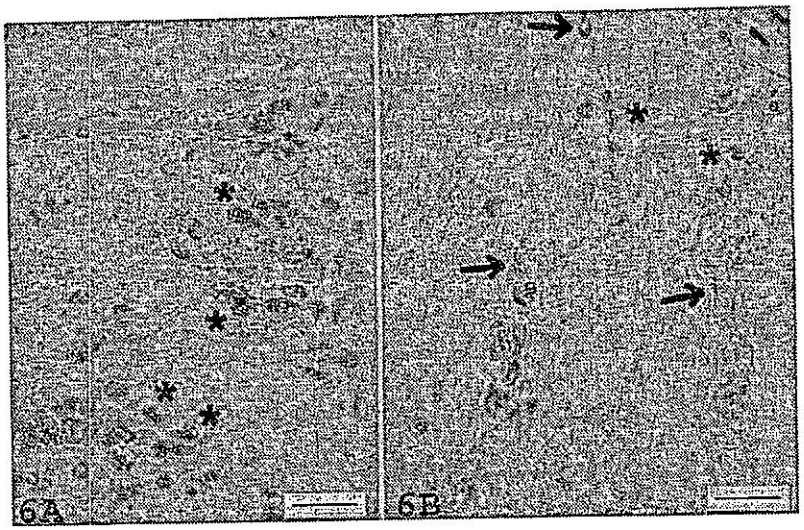

Fig. 6. (A) Numerous 5-HT positive cells (*) in the mesovarium in a 60-day-old rat and (B) 5-HT positive cells (*) and rare 5-HT positive fibers (→) in the oviductal tela subserosae in a 60-day-old rat. (Bar=21μm)

DISCUSSION

The definition of neurotransmitters is constantly changing as new discoveries are made concerning the nature of their action (Brown, 1994). Recent studies indicate that neurotransmitters are involved in the regulation of basic developmental processes such as cell proliferation, migration, differentiation and morphogenesis already in the pre-nervous period. For these actions neurotransmitters use similar receptors, transporters and signal transduction mechanisms as in mature neurons (Buznikov *et. al,* 2001).

It is known today that the ovary contains fibres of the adrenergic and cholinergic autonomic nervous systems. However, Lawrence and Burden (1980) found that ovarian denervation reduces but does not eliminate the content of noradrenalin (NA), which suggests the existence of an intrinsic source of catecholaminergic synthesis. The presence of tyrosine-hydroxylase, the enzyme necessary for NA biosynthesis, as described for neuronal cell bodies in the ovaries of Wistar rats (D'Albora *et. al.* 2000), monkeys (Dees *et al.,* 1995) and humans (Anesetti *et al.,* 2001), confirmed this assumption. Ovarian neurons were identified in Wistar rats by their morphology and by the expression of NeuN (a neuron-specific nuclear protein), from 14 h after birth to 50 days of age. However, neuronal perikaria were present in the ovarian hilum and medulla during the entire investigated period, but neurons first appeared in the cortex during postnatal days 10-20 (D'Albora et.al. 2000).

In our study using a histoflourescence method for monoamine visualization, a network of nerve fibers was found underlying the surface epithelium, in

interfollicular tissue and around blood vessels in ovaries from 15-day-old rats. Our results support the observations of Owman and Sjoberg, (1966) in rabbit ovary and Stefenson *et al.* (1981) in several other mammalian species. The rat is born neurologically immature, with major growth and differentiation of the autonomic nervous system occurring during early postnatal life (Black, 1982). During neonatal development the concentrations of catecholamines in the ovaries are subjected to regulation by circulating pituitary hormones (Ben-Jonathan *et. al.*, 1984), with a temporal relationship between plasma gonadotrophins, particularly FSH, and changes in ovarian NA concentration. Plasma FSH concentration was significantly elevated between days 10 and 20, whereas the major rise in plasma LH occurred between days 25 and 40. NA concentration increased markedly between days 20 and 35 of life. The changes in distribution and intensity of fluorescence obtained during the investigated period of development in our study were in accordance with these results. Marchetti *et al.* (1987) proposed that NA recognized by β-adrenergic receptors is involved in the regulation of specific functions of the ovary. Receptor concentration increases progressively between days 12 and 27 (mostly localized in the interstitial cells), reaching a peak value at 37 days of age (in the interstitial cells and corpora lutea). The increase in concentration of NA is in agreement with the density of adrenergic nerve fibers observed in our experiment in ovaries from 30-day-old females.

In addition, fine fluorescent fibers were observed in the region of the ovary with numerous primary follicles. In some of these follicles granular fluorescence was noticed between cells. Since initiation of follicular growth is a gonadotrophin-independent phenomenon, Mayerhofer *et al.* (1997) proposed that the follicles that begin to grow in highly innervated ovarian regions may have a selective advantage over those not exposed to neurotransmitter-activated, cAMP-dependent signals. According to this, NA, the most abundant catecholamine in the mammalian ovary, was the first representative of adrenergic innervation in the ovary identified as an intraovarian signaling molecule involved in the acquisition of gonadotrophin receptors (Bahr and Ben-Jonathan, 1985).

It is documented that catecholamines regulate myogenic tonus of the ovarian vasculature (Spicer, 1986) binding to α-adrenoreceptors (Kotwica 1992). The distribution of nerve fibres (around follicles and between secondary interstitial cells near large follicles) in the ovary and the fact that sympathetic mechanisms regulate contraction of the follicular wall and increase the intra follicular pressure, suggest a role for them in follicular development and ovulation (Savchenko *et al.* 1995).

Little is known about the potential contribution of DA to ovarian physiology. It was demonstrated previously that treatment with β-adrenoreceptor antagonist blocked the stimulatory effect of DA on human granulosa cells, which indicates that the effect of this catecholamine is indirect and most likely mediated by NA (Bodis et al., 1993). However, recent studies demonstrated that DA is not a step in the synthesis of NA only, but it exerts its own effects. In the human ovary and in cultured human granulosa luteal cells these effects are achieved through dopamine D1 receptor-mediated activation of cAMP-dependent protein kinase (Mayerhofer *et al.*, 1999, 2000). On the other hand, *in situ* hybridization revealed the existence of dopamine β-hydroxylase and DA transporter gene in primate oocytes, which indicates the ability of these cells to metabolize exogenous DA into NA (Mayerhofer *et al.*, 1998).

In our experiment, DA-positive structures were demonstrated *in situ*. In the ovaries of all studied groups weakly stained fibers were found around small follicles and between secondary interstitial cells. In addition, in 30- and 60-day-old animals bundles of DA-positive fibers and a few DA-positive cells were seen in the ovarian cortex as well as DA-positive fibers in the tela subserosa of the oviduct. Distribution of these immunolabelled dopaminergic fibers and cells was in accordance with the distribution of total monoaminergic structures that were detected using histofluorescence. However, the density of DA-positive structures labeled with DA antibodies was lower compared to total catecholamine positive structures detected by the fluorescence method.

Examination of 5-HT positive structures revealed that the major part of immunostained material was confined to the cellular compartment. However, in 15- and 30-day-old females 5-HT positive cells were absent while delicate 5-HT positive fibers were seen in the ovaries of all examined groups. Compared to other relevant data (Amenta *et al.* 1992) our observation about widespread 5-HT positive cells in the hilum, medulla, mesovarium and mesosalpinx of 60-day-old animals in estrous suggests that this indoleamine is important in regulation of the estrous cycle. Data obtained from *in vitro* experiments confirmed the stimulatory action of 5-HT on progesterone synthesis in luteal cells (Battista and Condon, 1986) and estradiol synthesis in rat preovulatory follicles (Tanaka *et al.* 1993). Bodis *et al.* (1992), found a high concentration of 5-HT in ovarian follicular fluid, which fluctuated according to the phase of follicular development in women.

The predominantly (intra)cellular localization of 5-HT in female reproductive organs suggests the possibility that these cells might be a local source of 5-HT. Our results, which are in accordance with those of Amenta *et al.* (1992), reveal that most 5-HT cells are mast cells (unpublished observation). This finding could mean that mast cells contain 5-HT only in cycling rats. Jaiswal and Krishna, (1996) suggest that the number and character of mast cells change during the estrous cycle. They showed that the number of mast cells in the whole ovarian complex of mice increases following FSH and oestradiol treatment.

In conclusion, our results support the hypothesis that the neurotransmitter supply of the ovary and oviduct is not exclusively via extrinsic innervation, but that intragonadal sources also have an important role in their synthesis. Considering all mentioned results relating to neurotransmitters in the ovary and oviduct, it appears that each monoamine neurotransmitter has (also) its own source in the ovary along with the neural supply. These observations support the opinion that a dynamic balance of different neurotransmitters, other intraovarian factors and hypothalamo-pituitary hormones is necessary for normal development and function of the ovary.

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LOKALIZACIJA MONOAMINSKIH NEUROTRANSMITERA U JAJNICIMA I JAJOVODIMA PACOVA TOKOM POLNOG SAZREVANJA

RADOVANOVIĆ ANITA, MIĆIĆ MILEVA i GLEDIĆ D

SADRŽAJ

Cilj našeg rada je bio ispitivanje lokalizacije i distribucije struktura pozitivnih na monoaminske neurotransmitere u jajnicima i jajovodima pacova. Za identifikaciju neurotransmitera u jajnicima i jajovodima 15, 30 i 60 dana starih AO pacova koristili smo histofluorescenciju (ukupni monoamini) i imunocitohemiju (dopamin i serotonin). Pozitivne monoaminergičke strukture prisutne su između folikula, naročito oko primarnih folikula, kao i između sekundarnih intersticijalnih ćelija. U mezoovarijumu i jajovodu 30 i 60 dana starih životinja zapažaju se fluorescentne ćelije i vlakna. Dopaminergične strukture su prisutne na istim mestima, ali njihova gustina je manja ako se uporede sa strukturama pozitivnim na ukupne monoamine. Retka serotonin-pozitivna vlakna zapažaju se uglavnom ispod klicinog epitela i u intersticijumu između kore i srži jajnika. Kod 30 i 60 dana starih ženki u hilusu i srži, pretežno oko krvnih sudova, nalaze se serotonin pozitivne ćelije, dok se u mezoovarijumu i jajovodu nalazi gusta populacija pozitivnih ćelija. Ni jednom od primenjenih metoda nije uočeno prisustvo monoamina u žutom telu.

Naši rezultati potvrđuju da neurotransmiteri u jajnicima i jajovodima ne potiču samo iz nervnih terminala, već da značajnu ulogu u njihovoj sintezi imaju intragonadalni izvori. Lokalizacija ovih elemenata pokazuje da monoaminski neurotransmiteri mogu ispoljavati direktan ili indirektan uticaj na funkciju jajnika.