PERIPHERAL SEROTONIN AND TRYPTOPHAN LEVELS IN RATS UNDER PROGESTERONE LONG-TERM ADMINISTRATION

Tryptophan and serotonin levels in duodenum mucosa and blood serum of rats under progesterone long-term administration have been determined. The studies show that tryptophan and the serotonin content increase in rats under progesterone long-term administration compared with control group of rats. Obtained data give evidence that biosynthetic pathway of serotonin, particularly, content of serotonin, is involved in the obesity development induced by progesterone long-term administration.

Key words: tryptophan, serotonin, progesterone, obesity.

Introduction. Obesity is one of the major health concerns in the 21st century and is one of the leading causes of preventable death [1]. According to the WHO 13% of the adult world population suffering from obesity (WHO, 2014). Some causes of the obesity development is associated with certain endocrine diseases, central nervous system disorders, and other illnesses [2, 3]. A lack of the accurate and scientifically recognized explanation of the mechanism of the body fat increase causes a difficult situation being currently present in the obesity treatment.

Progesterone, neuroactive steroid, is a female reproductive hormone. The major functions of progesterone are in the preparation of the uterus for implantation and maintenance of pregnancy. Progesterone is produced primarily by the corpus luteum of the ovary in normally menstruating women and to a lesser extent by the adrenal cortex [4]. At approximately the 6th week of pregnancy, the placenta becomes the major producer of progesterone [5-7]. Available literature data give evidence that there is a correlation between the progesterone excess and eating or affective disorders [8]. Progesterone launched in a woman’s body artificially (as contraceptives or for the hormone replacement therapy) has the same fat accumulation effect as the natural hormone during pregnancy [9]. Recent studies also show that progesterone makes such effects leading to many changes in neurotransmitter levels, particularly, in the serotonin level [10]. The latter can be important for the obesity development.

Serotonin is a monoaminergic neurotransmitter with activities that modulate central and peripheral functions. The first step in the synthesis of serotonin from tryptophan depends on the enzyme tryptophan hydroxylase, which is also the rate-limiting enzyme in its biosynthesis. Accumulating evidence indicates that peripheral serotonin plays an important role in glucose and lipid metabolism. Recent studies have shown that the level of blood serotonin and the number of intestine enterochromaffin cells in obese mice was found to be much higher than that in lean mice [11, 12]. Also was shown that serotonin regulates fat metabolism and feeding behavior through independent molecular mechanisms in Caenorhabditis elegans [13].

It is suggested that progesterone may affect on serotonin metabolism and functioning. To verify these hypotheses, we investigated the effect of progesterone long-term administration of rats on peripheral serotonin and tryptophan levels.

Materials and methods. White rats weighing 145-155 g were used in this study. The experiments met the basic requirements concerning the care and use of laboratory animals according to both the European convention for the protection of vertebrate animals used for experimental and other scientific purposes (Strasbourg, 1986) and ethical standards being in accordance with the legislation of Ukraine.

For experimental obesity to be developed the progesterone oil solution was administered subcutaneously (10 mg/kg body weight, treated daily for 28 days) following a procedure described in [12]. Rats belonged to the control group were injected with the oil used for the progesterone administration. All the animals were divided into two groups: 1 – normal control group; 2 – progesterone-induced obese group. To confirm the development of obesity, we have determined the body mass index and Li index. To determine the tryptophan and serotonin levels blood serum and duodenum were taken 28 days after the progesterone injection.

Both the tryptophan and the serotonin content were analyzed using ion exchange chromatographic method (KM-sepharose). The fluorescence of both the tryptophan and the serotonin eluate was measured at an excitation wavelength of 359 nm and 295 nm respectively and a fluorescence wavelength of 485 and 550 nm respectively using shimadzu spectrofluorophotometer (RF-1501) [13-15].

Statistical analysis of data was carried out by the software package 'Statistica 7.0'. For the analysis of data distribution type, Shapiro-Wilks criterion was used. As the data were normally distributed, we used Student's t test for independent samples. Mean values (M) and standard deviations (SD) were calculated. Significant difference was considered at p ≤ 0.05.

Results and discussion. We determined tryptophan and serotonin levels in duodenal mucosa of the rats under progesterone long-term administration. It has been established that the tryptophan level in the experimental group was 2.1 times greater than that of the control group (Fig. 1, A).
Serotonin was observed to increase by a factor of 1.5 in the experimental group as compared to the control group in studying serotonin content in duodenal mucosa of rats under progesterone long-term administration (Fig. 1, B). Increase in serotonin level could be due to the impaired function of enterochromaffin cells of the gastrointestinal tract and releasing serotonin in response to a food intake. Serotonin released by enterochromaffin cells can stimulate 5-HT3 receptors of the chemoreceptor trigger zone which produce impulses being transmitted to the vomiting center to initiate vomiting.

In blood almost whole pool of serotonin is located in storage vesicles of platelets and released under the influence of various stimuli, such as ADP, thrombin, collagen, and even serotonin. Serotonin removal from the circulatory system is caused by its inactivation in the liver or endocytosis in platelets and lung vascular endothelial cells. The next stage of our work was to investigate the tryptophan and serotonin levels in serum. Tryptophan and serotonin levels have increased in 1.5 and 4.1 times respectively in rats under progesterone long-term administration compared with control group of rats (Fig. 2).

Tryptophan that located in the extracellular matrix is transported to serotonergic neurons by means of the nonspecific membrane transporter, which is assumed to be involved in transport of a number of amino acids such as valine, leucine, and isoleucine. Therefore, the possible cause of the rise in tryptophan level in rat serum is a competition between tryptophan and other metabolites for ways of crossing the blood-brain barrier. An establishment of the serotonin increase could be accounted for a malfunction of the vascular and platelet phases of hemostasis since the platelets uptake a substantial portion of serotonin.

The results of this study have shown statistically significant changes in the tryptophan and serotonin levels in duodenal mucosa and serum of the rats under progesterone long-term administration. The findings indicate that biosynthetic pathway of serotonin is involved in the process of the obesity development. Taking into account this fact it would be promising to further investigate serotonin system functioning in the periphery and the CNS of rats under progesterone long-term administration.
ВМІСТ ПЕРИФЕРИЧНОГО СЕРОТОНІНУ ТА ТРИПТОФАНУ У ЩУРИВ
ЗА УМОВ ДОБРОТРИВАЛІВОГО ВВЕДЕННЯ ПРОГЕСТЕРОНУ

Було визначено вміст триптофану та серотоніну в слізовій оболонці 12-палічча щурів та сироватці крові щурів за умови зазвичайного, індукованого введення прогестерону. Дослідження показали, що вміст триптофану та серотоніну в слізовій оболонці 12-палічча щурів та сироватці крові щурів проходили з різними темпами, але відмінності їх були виявлені в день індукованого введення прогестерону.

Ключові слова: триптофан, серотонін, прогестерон.

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СОДЕРЖАНИЕ ПЕРИФЕРИЧЕСКОГО СЕРОТОНИНА И ТРИПТОФАНА В КРЫС

Было определено содержание трифтора и серотонина в слюнной железе 12-челюстной крысы и крови под воздействием прогестерона. Исследования показали, что изменение содержания трифтора и серотонина в слюнной железе и крови крыс было индуцировано введением прогестерона, в сравнении с его контролем.

Ключевые слова: триптопан, серотонин, прогестерон.