

Caffeine is a natural alkaloid contained in leaves, seeds and fruits of at least 63 plant species. Natural sources of caffeine, including coffee beans, tea leaves, kola nuts, bissu nuts, cacao beans, guarana, and mate, are used as ingredients in food, beverages, herbal supplements and medications. Caffeine is well absorbed in the gastrointestinal tract and rapidly distributed to other tissues. It also easily crosses the blood-brain barrier by simple diffusion or by active transport.

A reproductive process in female is under the control of the neurohormonal system called the hypothalamic-pituitary-gonadal axis. The hypothalamus, as the highest level of this axis plays a primary role in the regulation of reproduction, which is conditioned by uninterrupted tonic secretion of neuropeptide – gonadotropin-releasing hormone (GnRH), which regulates the synthesis and release of gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. Secretory activity of GnRH-ergic neurons is regulated by a number of neural circuits that may both stimulate or inhibit the secretion of GnRH. The most important neurotransmitters that modulate the secretion of GnRH are noradrenaline, dopamine and serotonin. The presence of adenosine and ryanodine receptors by which caffeine exerts its biological effects was found both in the hypothalamus and pituitary gland. *In vitro* studies suggest the involvement of these two groups of receptors in the regulation of LH and FSH secretion from the gonadotropic cells. Therefore it appears that caffeine by interacting with adenosine and ryanodine receptors may affect the activity of the HPG axis at the level of hypothalamus and pituitary. The *in vitro* study showed that facilitation of Ca^{2+} release from the intracellular store by caffeine stimulates the secretion of GnRH. It was previously found that exposure to caffeine increased LH and decreased FSH serum levels in adult Swiss albino female mice. In contrast, daily administration of caffeine (30 or 60 mg/kg) to mature male rabbits caused an increase in plasma FSH and a decrease in plasma LH. There is a prevailing view of the negative impact of caffeine on fertility in women. It is supported by a large part of the studies analyzing the relationship between caffeine consumption by women in childbearing age and the incidences of their difficulty in becoming pregnant. It was described that among women who attempted to become pregnant for 3 months, the high caffeine consumers (i.e. ≥ 1 cup of brewed coffee/day) were significantly less likely to become pregnant in each cycle than the lower caffeine consumers. In the extensive research, which involved women from five European countries including Poland, a relationship between increased caffeine consumption and a reduction in fertility was also showed. However, in the study carried out in the United States, which was attended by nearly three thousand women, no correlation between caffeine consumption and a reduction in fertility was found.

It is also worth noting that the response of HPG axis to caffeine may be dependent on the immune status of the organism, because inflammation is often associated with increased expression of adenosine and ryanodine receptors, which may enhance the physiological effects of caffeine. Furthermore, caffeine has pro-inflammatory properties. It was found that caffeine increased synthesis of pro-inflammatory cytokines simultaneously suppressing the synthesis of anti-inflammatory cytokines. Our previous study demonstrated that the inflammation caused by bacterial endotoxin – lipopolysaccharide (LPS) inhibits the secretion of GnRH/LH in ewe, and pro-inflammatory cytokines appear to play a leading role in interactions between the neuroendocrine and immune systems. Therefore it may be assumed that caffeine disturbing the course of endogenous anti-inflammatory processes, may intensify the negative effect of inflammation on the secretion of GnRH/LH.

Therefore, the aim of the project is to investigate the influence of the peripheral and central administration of caffeine on the secretion of GnRH/LH in ewes in the physiological state and during immune stress. Central injection of caffeine into the third ventricle of the brain will enable the investigation of its ability to modulate the reproduction processes directly at the level of the hypothalamus.

The present study is a basic research, and its goal is better understanding of the mechanisms by which caffeine may modulate the process of reproduction in female at the level of the central nervous system. However, the obtained data will also demonstrate whether the immune status of the organism may influence the strength and character of the caffeine action. Therefore, the results of this study may be useful for both human and veterinary medicine. As there are differences between the rate of metabolism of caffeine in sheep and humans, the results of this study cannot be easily extrapolated to the human organism. However, surely they can serve as the basis for research focused on the effect of caffeine consumption by women on the course of ovulation cycle in relation to their state of health.