Oxytocin and kisspeptin interactions and functions in female rats with induced diabetes type 2

Obesity is one of the most common health problems in the modern world. According to the World Health Organization (WHO), obesity and its co-morbidities are the leading cause of death in highly developed countries. The statistics are appalling – in these countries more people are dying because of obesity and associated diseases (type 2 diabetes, certain types of cancer, cardiovascular diseases, reproductive dysfunctions) than due to malnutrition. Over 650 million people worldwide suffer from obesity. Although obesity can be prevented by changing the lifestyle and limiting the consumption of carbohydrates and fats, available studies show that it is very difficult for patients to change their habits. Therefore, scientists are currently trying to explain the physiological processes underlying obesity and/or type 2 diabetes, in order to be able to develop more effective therapies in the future to reduce body weight, and thus the risk of obesity-related diseases. One of the potential weapons in the fight against obesity may be a well-known hormone – **oxytocin**.

Oxytocin is involved in reproductive processes. It is responsible, for example, for uterine contractions during delivery (it can be given to induce labor) and is a factor involved in milk production. Oxytocin also participates in emotional reactions - it is the so-called "hormone of love". However, studies carried out in recent years on laboratory animals have shown another role for oxytocin - it takes part in the regulation of food intake and body weight. Oxytocin administration reduces food intake. So far, the first clinical trials have been carried out – the administration of oxytocin in the form of nasal drops reduces appetite in humans. The positive effect of this hormone was also demonstrated in genetic animal models of type 2 diabetes – *ob/ob* (mutation within the leptin receptor gene) and *db/db* mice (mutation within the leptin gene). However, similar studies are not available for models with experimentally induced type 2 diabetes, where obese animals (eating a high-fat diet) are given a toxin, streptozotocin (STZ), which destroys pancreatic islets. The phenotype of diabetes in these animals resembles that of a human. It would be worth examining how the administration of oxytocin to diabetic females (so far studies are mainly conducted on males) would affect the diabetic phenotype. Oxytocin is present not only in the brain, but also in peripheral tissues involved in the regulation of the body's energy expenditure. So far, it has been shown that the main “target” of oxytocin is adipose tissue. Studies have shown that long-term administration of oxytocin to obese animals significantly reduces fat mass. In addition, effects associated with the administration of this hormone were also observed in the pancreas and liver. Oxytocin administration stimulates the secretion of insulin and glucagon, the hormones that regulate the level of blood glucose. However, similar studies have not been carried out in the experimental model of obesity and diabetes.

As mentioned at the beginning, obesity and diabetes can lead to dysfunction of the fertility system. One of the factors that plays a key role in the regulation of reproductive capacity is **kisspeptin (KP)**, discovered in 2003. In recent years, it has been shown that KP may be a potential link connecting metabolic status and reproduction. Both in obesity and in malnutrition there is a decrease in levels of KP in the region of the brain called hypothalamus, which may reduce the reproductive capacity of the body. It has also been shown that disturbances in the production of KP occur in animals with induced diabetes. Moreover, the role of KP has been shown not only in the brain, but – like oxytocin’s – also in peripheral tissues related to metabolism (pancreas, liver and adipose tissue). For example, KP enhances insulin secretion from the pancreas as well as plays a protective role on liver cells – hepatocytes. But, these studies were carried out mainly on males. There are few reports indicating gender differences in the response of KP (both peripherally and centrally) to type 2 diabetes.

Recent studies show that KP receptors are present on the oxytocin-releasing neurons located in the paraventricular nucleus of the hypothalamus (PVN). In addition, preliminary studies show that kisspeptin and oxytocin neurons contact though varicosities with each other. Therefore, it is possible that both peptides "work” together in the regulation of the body's energy balance. This project will determine the effect(s) of chronic oxytocin administration on kisspeptin (both in the brain and periphery); it could lead to the discovery of new mechanism(s) involved in the regulation of metabolism. In addition, most of the research is carried out on males – conducting studies on females could also answer the question of whether there are significant sex differences in the response of the kisspeptin system to the oxytocin. The results of this study could, in the future, help in the development of new, more effective strategies in therapy of obesity and/or diabetes.