The current **obesity epidemic** is thought to be largely attributable to excessive consumption of foods, which are high in sugars and saturated fats, and the lack of or very limited physical activity. Inadequate diet and reduced physical activity could contribute to a range of metabolic disturbances including type 2 diabetes (diabetes mellitus 2 - DM2). Importantly, DM2 accounts for 90% of diabetes cases reported around the world and is often associated with obesity. As obesity and diabetes are widespread throughout the globe, the World Health Organization (WHO) recognized both diseases as among the biggest public health problems. The WHO report states that every year about 2.8 million die due to obesity and its consequences. Moreover, the International Diabetes Federation estimated an overall prevalence of diabetes to be 382 million today, and predicted a rise to 471 million by 2035. Because of escalation of obesity (in the US one of three people is obese) there is a pressing need for further research in this field. In Poland about 64% of men and 49% of women have extended body mass (body mass index BMI above 25%). This problem is of particular concern as it is reaching the younger generation. In Poland in the 1970s, less than 10% children had weight problems but now every fifth child is overweight.
Besides primary metabolic health problems occurring in people with obesity and diabetes, there are numerous secondary problems, including major disruptions of the reproductive system, manifested by disrupted menstrual cycles in women, decreased testosterone levels and spermatogenesis in men, hypogonadism, premature child birth, miscarriages and infertility. In Eastern Europe and America, about 50% of women are overweight. In the light of the increased incidence of obesity and diabetes, and increased infertility in modern society, there is need to conduct research in this area. There is still a fundamental lack of synthetic knowledge considering integration of metabolic and reproductive systems in obese and diabetic patients. Basic research is essential if we are to uncover the mechanisms responsible for metabolic and reproductive failure in cases of obesity and diabetes.

Reproduction is influenced by metabolic cues and is governed by the hypothalamic-pituitary-gonadal (HPG axis). The hypothalamus is situated on top of the axis and neurons in this region synthesize and secrete gonadotropin-releasing hormone (GnRH). In response to GnRH, the anterior pituitary secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gonadotropins regulate folliculogenesis in females, spermatogenesis in males, and steroid biosynthesis in both sexes. The gonads also release sex steroid hormones (estrogens, progestins, and androgens). Although each level of the HPG axis is critical for regulation of reproductive functions, the master molecule of reproduction, GnRH, is the primary regulator of the entire system.

In 1977 the **Nobel Prize in Physiology or Medicine** was awarded for discoveries concerning the peptide hormone production in the brain involved in the regulation of reproductive function. However, for a long time there was a paucity of information on possible neurons that convey information from sex hormones onto GnRH neurons, as the latter do not possess receptors for sex hormones critical for regulation of reproductive function. In 2003, the field of reproduction was revolutionized by discovery of the role of kisspeptin (encoded by Kiss1 gene) and its receptor (KiSS1 R or GPR54) in the regulation of the reproductive function. Both in humans and mice, mutations in the KiSS-1 R gene were associated with hypogonadotrophic hypogonadism, a condition characterized by low sex steroid and gonadotropin levels, and a failure to enter puberty. Kisspeptin cells co-express sex hormone receptors, suggesting that they are important mediators of hormonal feedback onto the GnRH system. Recent studies have also shown that kisspeptin plays an important role in the integration of metabolic and reproductive systems in the brain. Moreover, changes in metabolic status can lead to disruption of the reproductive systems at multiple levels, e.g. the secretion of GnRH, LH, FSH, and sex steroids (estrogen, testosterone and progesterone), and in the most severe cases can lead to infertility.
Recent data indicates that kisspeptin does not act alone to regulate reproduction. A subset of neurons was identified in the arcuate nucleus of the hypothalamus (ARC) that co-localize, in addition to kisspeptin, the neuropeptides, neurokinin B (NKB), and dynorphin (DYN). Because of the almost complete colocalization of all three peptides in this population, they have been called “KNDy” (kisspeptin, neurokinin B, dynorphin) neurons. KNDy neurons appear to play an important role in the integration of metabolic and reproductive function, and there has been much recent attention to the signaling of metabolic cues such as leptin and insulin through KNDy cells.
The main goal of this project is to gain knowledge about mechanism(s) responsible for disruptions of reproduction in female rat models of diet induced obesity (DIO), and diabetes type 2 (DM2). KNDy neurons work together with other neurons to establish functional circuits that control reproduction. However, in case of obesity and DM2 these circuits may be disrupted resulting in functional consequences for both reproductive and metabolic functions. Thus, we hypothesize that alterations in KNDy neurons and their peptides play a central role (at the level of the brain) in mediating reproductive and metabolic abnormalities in DIO and DM2 female rats. We will use immunocytochemistry (to study peptides) and in situ hybridization and PCR (to study mRNA) to reveal alterations in the expression of KNDy peptides and their receptors, and associated changes in hormonal and metabolic profiles of DIO and DM2 females. Moreover, we will employ ovariectomy with estradiol and/or progesterone replacement to explore the possible deficits in steroidal regulation of KNDy peptides in DIO and DM2 females. Finally, we will use pharmacological approaches (tachykinin agonists) to study the role of NKB and other tachykinins: NKA and substance P (SP) in the control of gonadotropin secretion in DIO, DM2 and control animals.

This project represent a novel approach as these rat models of diet-induced obesity (DIO) and diabetes type 2 (DM2) have not previously been systematically explored in terms of possible alterations in KNDy neuron function, hormonal and metabolic profiles. We believe that the basic knowledge obtained in the course of realization of this project will allow in the future to translate this research to clinical practice and applications to veterinary medicine. Manipulations of the KNDy system could serve as a promising strategy in translational research with the possibility of future clinical application to regulate reproductive problems in obese and diabetic patients.