Summary in English

Overweight and obesity are classified as lifestyle diseases. Nowadays, it has become popular to consume highly processed products characterized by a high content of fats, simple sugars, and salt. This type of diet is called the Western-style diet or, in animal studies, the cafeteria diet (CAF). Animals kept on the CAF diet receive products available in stores. Long-term consumption of this diet leads to excessive accumulation of adipose tissue, disturbances in the hormonal metabolic profile, and the development of inflammation in the body.

Moreover, according to the theory of prenatal programming, the predisposition to disorders caused by an unhealthy diet can be passed down from generation to generation. The mother's nutritional environment during pregnancy may affect the onset of health problems in the offspring, which will persist even into adulthood. In addition, an improper maternal diet disturbs the functions of the reproductive system of the offspring. Although the mechanisms responsible for these processes still need to be better understood.

Reproduction is regulated by the hypothalamic-pituitary-gonadal (HPG) axis. An important bridge between metabolic and reproductive functions is kisspeptin (KP), a peptide expressed in both the hypothalamus and peripheral tissues. It acts via the GPR54 (*Kiss1r*) receptor and is known as the most potent activator of the HPG axis. In the arcuate nucleus of the hypothalamus, in addition to KP-expressing neurons, the neurons expressing two other peptides - neurokinin B and dynorphin A are present. These neurons are called KNDy, from first letters of names neuropeptides (kisspeptin/neurokinin B/dynorphin A).

In addition, sirtuin 1 (SIRT1) is a critical element of the epigenetic machinery that regulates the processes of sexual maturation by transmitting information about the body's metabolic state to KNDy neurons.

The following hypotheses were tested:

1) **Maternal CAF administered before pregnancy and during pregnancy and lactation affects in a sex-dependent manner the weight and body composition of the offspring.**
2) **Maternal CAF administered before pregnancy and during pregnancy and lactation alters metabolic, hormonal, immunological profile and reproductive functions of offspring in sex-specific manner.**

3) **The *Sirt1/Kiss1* system in the hypothalamus and/or liver at least partly contributes to the observed metabolic changes and reproductive disorders of the offspring caused by maternal CAF.**

The short-term (10 weeks, experiment 1) and long-term (16 weeks, experiment 2) effects of the mother's CAF on the offspring were studied.

In order to test the above hypotheses, the effects of the maternal CAF on the metabolic, hormonal, and immunological profile were investigated using ELISA assays and mRNA transcript levels (rt-PCR) for pubertal and reproductive genes in both the hypothalamus and the liver. The results of this doctoral dissertation were based on two experiments carried out on female Wistar rats and their offspring. Two groups of animals were studied: a group with metabolic disorders induced by the cafeteria diet (CAF), composed of commercially available products with a high content of carbohydrates and fats, and a control group (C), which received the AIN93G semi-synthetic diet.

In experiment no. 1 - short-term exposure to maternal diet - females were kept on CAF for 4 weeks before conception and during pregnancy (21 days) and lactation (21 days). On postnatal day 3 (PND 3), the offspring were weighed and sexed. On PND 25, the offspring of CAF and C mothers were weighed and examined for body composition and fat content. The offspring were euthanized on that day, and tissues were collected for further analysis (blood, brain, and liver).

In experiment no. 2 - long-term exposure to maternal diet, females received CAF for 10 weeks before conception, during pregnancy, and lactation. After weaning, offspring were fed a control semi-synthetic AIN93G diet. Tissues (blood, brain, and liver) were collected from the offspring at three-time points: for females 30, 35, and 65 days of age; for males at 40, 45, and 65 days. In addition, at the time mentioned above, the offspring were weighed and examined for body composition and fat content.

In order to assess the impact of the mother's CAF on the offspring, the following analyzes were carried out: the metabolic profile, i.e., the level of glucose, insulin, cholesterol, and triglycerides, was assessed (experiments 1 and 2). The immunological profile was assessed: levels of interleukin 6 (IL-6), interleukin 10 (IL-10), and tumor necrosis factor α (TNF-α) (experiment no 1). Hormonal status was assessed based on the level of estradiol (for females), testosterone (for males), and luteinizing hormone (for both sexes) (experiment no 2).Transcript levels for *Kiss1, Gpr54, Sirt1, Pdyn* and *Tac2* in the hypothalamus and *Kiss1, Gpr54* and *Sirt1*

in the liver were checked (experiment 1 and 2). In addition, in experiment no 2, mRNA levels for *Pdyn* and *Tac2* in the hypothalamus were examined. Moreover, in experiment no 2, vaginal opening in female offspring was analyzed as an external marker of the onset of puberty.

Based on the conducted experiments, the following results were obtained:

Experiment no 1: 1) A reduced body weight and a higher fat percentage characterized the offspring of CAF mothers on PND 25. **2)** The maternal CAF affected in a sex-specific manner: **i)** the metabolic profile of the offspring on PND 25, and these effects were prominent in the female offspring; **ii)** the immune profile of the offspring (levels of Il-6, IL-10, and TNF-α), and the effects of the diet were more robust in females. **3)** It was shown for the first time that the mother's CAF leads to sex-dependent changes in the level of mRNA transcript for *Kiss1* in the hypothalamus and the level of mRNA for *Kiss1* and Sirt1 in the liver of the offspring at very early stages of development, already on PND 25.

Experiment no 2: 1) Offspring (both females and males) in the long-term exposure study of mothers on the CAF had reduced body weight. Additionally, female offspring have altered body composition. **2)** Mother's CAF resulted in: **i)** increased cholesterol and triglyceride levels and sex-specific changes in glucose and insulin levels. In addition, CAF males had elevated LH levels on PNDs 45 and 60 compared to PND 40; **3)** Females from CAF dams showed a three-day delay in onset of sexual maturation compared to group C. **4)** Sex-dependent changes in mRNA levels for *Kiss1*, *Gpr54* and *Sirt1* in the hypothalamus and *Kiss1* and *Sirt1* in the liver were also observed: **ii)** CAF females had a lower level of mRNA for *Sirt1* in the hypothalamus on PNDs 30 and 35 compared to PND 60. **ii)** CAF males on PND 45 were characterized by reduced transcript levels for *Gpr54* 1 in the hypothalamus and *Sirt1* in the liver on PND 45 compared to C group.

The following conclusions were drawn from both experiments:

1) The offspring of CAF mothers are characterized by reduced body weight and body composition disorders.
2) Exposure to the CAF before pregnancy, during prenatal and early postnatal periods leads to sex-specific changes in the offspring's metabolic, hormonal, and immunological profiles.
3) Female offspring are more sensitive to the effects of short-term exposure to the mother's CAF when assessing metabolic and immunological parameters.

4) It has been proven for the first time that already at the very early stages of development, i.e., PND 25, the mother's CAF leads to sex-dependent changes in the level of mRNA for *Kiss1* in the hypothalamus and the level of mRNA for *Kiss1* and *Sirt1* in the liver of the offspring.
5) It has been shown for the first time that long-term exposure to the CAF before pregnancy, and during prenatal and early postnatal periods diet delay sexual maturation in female offspring.
6) Changes in the *Sirt1/Kiss1* system in the hypothalamus and the offspring's liver may contribute to the observed sex-specific metabolic effects and reproductive system dysfunction caused by exposure to the mother's CAF.

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