

## **1. Research project objectives**

According to the "Fetal Programming Hypothesis" proposed by Dr. David Barker, environmental factors, such as the mother's diet during pregnancy and lactation, determine the pathologies that appear later in life. Improper nutrition of the mother (high-/low-carbohydrate, -protein or -fat diet) may predispose to the development of obesity, type 2 diabetes, depression and enhanced impulsivity. These factors, in turn, may increase susceptibility to substance abuse and consequently lead to drug use disorder.

Translational research suggests that high-fat diet in adolescence and adulthood may induce disturbances in the functioning of the brain, including addiction to psychoactive substances. So far, preclinical studies have also shown that maternal diet changes the phenotype of both adolescent and adult animals for palatable food, alcohol or nicotine. There is no data on the relationship between the type of food consumed by the mother and vulnerability to the development of cocaine use disorder in the offspring.

The aim of the project is to analyze the mechanisms, that involve melanocortin type 4 receptors (MC4Rs), and that determine the phenotype prone to cocaine in adolescent rat offspring whose mothers were fed a different diet. We aim to explore the effect of high-fat, high-carbohydrate and mixed diet during pregnancy and lactation on the development of sex-dependent cocaine addiction phenotype. In addition, we will evaluate the role of MC4Rs in the acquisition and maintenance of cocaine abuse, as well as the reinstatement of drug-seeking behavior. We will also answer whether a mother's diet may induce adaptive changes within the MC4Rs and whether these receptors may be a biomarker of the mechanisms that predispose to cocaine use disorder.

## **2. What kind of research will be performed**

The behavioral, molecular and pharmacological studies will be performed at the Laboratory of Drug Addiction Pharmacology of the Institute of Pharmacology Polish Academy of Sciences. Behavioral procedures include the measurement of locomotor activity, forced swimming test, elevated zero maze test and novel object recognition test, the study of impulsive behavior, assessment of palatable food intake, as well as intravenous cocaine self-administration and extinction/reinstatement to cocaine-seeking behavior. Molecular and neurochemical analyses include Triton-soluble and -insoluble fraction (TIF) and assessment of protein expression by Western Blot analysis as well as surface receptor cross-linking with BS<sup>3</sup>.

Pharmacological manipulations involving administration of agonists and antagonists of MC4Rs and administration of viral vectors in order to silence or enhance its expression will assess the role of MC4Rs in different phases of cocaine addiction.

## **3. Reasons for choosing the research project**

Substance use disorder is a serious disease of the central nervous system, on which many researchers have concentrated for many years because of its destructive nature and unsatisfactory therapeutic effects. However, the complex basis of the disease hampered knowing and understanding its neurobiological mechanisms. In the proposed project, using the experimental animals, we decided to investigate whether the mother's diet can affect the development of the phenotype vulnerable to cocaine use disorder, and whether pharmacological manipulations may alter the response to the psychoactive substance. If the tested hypotheses, regarding the involvement of MC4 receptors in the development of addiction will be confirmed in the project, then the results will point to new research directions in the development of targeted pharmacotherapy for cocaine addiction. We believe that our multi-faceted preclinical project may help to develop appropriate dietary recommendations for mothers, which in turn may reduce the frequency of substance abuse-prone phenotype in the offspring.

Similarly to abused drugs, natural rewards (e.g., food, sex) produce adaptive behaviors in the brain, thus, the results may lead to the discovery of new "general" therapeutic strategies. Therefore, the results of this project may have a great impact on the reduction of medical, social and economic harms in the future.