

In recent years impaired fertility and male infertility are growing social problems. Under the development of these diseases lies among others endocrine and genetic factors as well as environmental factors (exposure on chemicals and stress). Clinical and biological studies revealed mainly abnormalities in sperm production but also morpho-functional disturbances in Leydig cells, such as alterations in steroidogenesis (production of sex hormones) and development of tumors (Leydigoma). Diagnosis of the causes of male infertility is often difficult, due to incomplete knowledge about hormonal and genetic control of testis function.

The most important function of Leydig cell is production of androgens. In mammals, including humans, the presence of two Leydig cell populations has been confirmed. Fetal population is responsible for hormonal control of the male reproductive system differentiation and testis descent into the scrotum. After birth fetal cells are replaced by cells of adult population which will control the male sex characteristic and function of the reproductive system later in life including aging. Role of estrogens in male gonad is still not well understood. It is known that both deficiency or excess of estrogen results in severe morphological alterations of spermatogenic cells as well as somatic cells (supporting cells and steroidogenic cells, respectively). Moreover, function of somatic cells is also disturbed. Previous studies have shown a proliferative, apoptotic and tumorigenic estrogenic properties. Although estrogens are produced in testicular cells throughout the male life including fetal development and aging, the mechanisms of their action and cellular processes that are regulated by estrogens in Leydig cells remain not well described.

The main objective of the project is to investigate the mechanisms of estrogen signaling in Leydig cells of fetal and adult populations with the participation of intracellular estrogen receptors: intracellular classical (ER and ER ) and related (ERR , ERR , ERR ) as well as membrane: G protein-coupled (GPR30). Moreover, the role of estrogen signaling in control of physiological and pathological cellular processes such as proliferation, differentiation, apoptosis and tumor transformation of Leydig cells will be explained.

A comprehensive study will be conducted in both in vitro and in vivo systems at the cellular and molecular level including epigenetic regulation. Leydig cells will be obtained from rodents (mouse, bank vole) and boars in different age: at birth, sexually immature, mature and aging. Studies in mice will be performed after blockade or activation (gene silencing techniques and pharmacologically) of estrogen receptors then the results will be verified in bank vole, in which there is a physiological reduction of estrogen levels and boar, in which intratesticular estrogen levels are physiologically high. Additionally, Wilms' tumor knockout mice (Wt1), will be used to examine tumor transformation of Leydig cells. Also, interaction of estrogens with a number of signaling pathways i.e. insulin-like peptide 3, relaxin, Wt1 and Desert hedge hog, which importance in control of Leydig cell function has recently been confirmed, will be studied.

Undertaken research in terms of endocrine, genetic and cytophysiological aspects requires a deep knowledge of the experimental andrology, biochemical endocrinology, cell biology and molecular genetics of reproduction together with professional experience in imaging techniques and work with laboratory and domestic animals. Elucidation of a comprehensive scientific problem as well as future research tasks will be possible through the establishment of research team with the highest and rare complementary competencies. Experienced scientists and students will learn from each other and actively cooperate also internationally under the management of highly qualified both scientifically and methodologically PI. We believe that our multifactorial approaches and passion will lead to development of novel solution and discovery of unknown biological events and research areas.