6 ABSTRACT

The mouse vas deferens protein is a known member of the aldo-keto reductase super-family and has been suggested to be involved in detoxifying processes. The enzyme is expressed in the murine *vas deferens*, the *zona fasciculata* of the *adrenal cortex* and in the ovary. While the expression in the *vas deferens* and in the adrenal gland is constitutive, a remarkable regulation of the protein expression exists in the ovary following the LH surge shortly before ovulation. The main substrates of MVDP were previously shown to be 4-hydroxynonenal and isocaproaldehyde, two cytotoxic compounds whose metabolism is essential for cell survival. The expression pattern and the substrate specificity of MVDP led to the hypothesis that this protein is involved in reproductive processes and steroidogenesis. The main objective of the presented work was to test this hypothesis by generating knockout mice deficient in MVDP function in order to analyse the *in vivo* protein function.

The established mouse model was viable and the targeted disruption failed to cause any reproductive dysfunction and had no significant influence on ovulation and spermatozoa quality in vivo, thus rebutting the above hypothesis. MVDP knockout mice, however, show remarkable sexually dimorphic phenotypes, which are most likely due to adrenal malfunction. The concentration of corticosteroid is elevated in male knockout animals and progesterone levels are increased in females mutants. Furthermore knockout female animals show expansion of the adrenal cortical layers and an increased body weight. Furthermore they respond to exogenous stimuli of inflammation with increased apoptotic cell death within the adrenal gland. A reduced body weight and a significantly higher mortality rate could be observed in male knockout animals. This mortality was shown not to be induced by acute stress, but could potentially be explained by chronic exposure to stress. In summary, MVDP knockout mice show gender specific alterations in adrenal cortex morphology, body weight, hormone levels, responses to inflammatory stress and mortality rates.

Moreover, the created mouse model with floxed *Mvdp* sequences (conditional knockout) might become a useful tool directing loss of function in a tissue specific manner and thus providing further insights into the nature of MVDP.