Abstract

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Title of diploma thesis: The impact of SIRT1 inhibition on zebrafish morphology and behavior

After discovery of connection between yeast Silent Information Regulator 2 (Sir2) and its ability to alter lifespan, Sir2 and its seven mammalian orthologs became very attractive therapeutic target. These so called sirtuins are members of a histone deacetylase family. They possess unique catalytic activity having nicotinamide adenine dinucleotide as a cofactor and their function can be influenced by environmental factors. The aim of this diploma thesis was to extend knowledge of Sirtuin 1 (SIRT1), which is from all mammalian sirtuins considered to have the closest relation to yeast Sir2. At first we tested the impact of SIRT1 inhibition on early developmental stages of zebrafish (*Danio rerio*) embryos and larvae, finding out that SIRT1 is important for normal development and SIRT1 inhibition or malfunction result in cardiovascular defects, delayed development, and death. Additionally, we tried to learn more about SIRT1 and its connection with Parkinson´s disease by combining nontoxic doses of SIRT1 inhibitor EX527 with 1-methyl-4-phenylpyridinium (MPP^+), drug known to induce Parkinson´s disease like symptoms. However, the SIRT1 down regulation not only failed to protect zebrafish embryos and larvae from MPP^+ toxicity, but even resulted in more severe phenotype, suggesting that SIRT1 inhibition might not be the right option of Parkinson´s disease therapy.