If only I could tell …

Summary

Our study with 3,5-diiodo-L-thyronine (T2), a thyroid hormone that was earlier regarded functionally inactive, has revealed its effects in the two-day tail suspension test. In this model, a bolus injection of T2 at two different doses, to mice of two different strains, resulted in a decrease of depressive-like behaviour, thus, suggesting the antidepressant-like effect of T2 **(Chapter 2)**. This effect of T2 was not known before; it suggested clinical use of T2 under conditions that require faster than with other thyroid hormones therapeutic effect. However, no effects of T2 on depressive-like behaviour were found in a classic two-day forced swim test **(Chapter 3)**. Thus, our results have demonstrated a limited sensitivity of the forced swim test that is in line with available literature, and suggested a need for its modification so the accuracy of the test could be increased.

In this context, we modified commonly used protocol of the forced swim test, where an additional session on Day 5 has followed the initial exposure on Days 1 and 2 in its classical variant **(Chapter 4)**. We hypothesized that additional delayed session on Day 5 can model increased contextual learning and consolidation of environmental adversities related to the testing. Increased brain expression of GSK3β, a hallmark of a distress and depression in humans was observed in mice after modified, but not classic sessions of the swim test **(Chapter 4)**. Moreover, increased scores of depressive-like behaviour (floating behaviour) during additional delayed testing positively correlated with the levels of GSK3β mRNA in the prefrontal cortex of experimental groups **(Chapter 4)**. No such correlations were found in the hippocampal formation, while GSK3β expression was increased there as well. Elevated activities of GSK3β during repeated but not single exposure to swimming were further demonstrated on a protein level. The concentration of 9-Ser-phosphorilated (inactive) form of pS9-GSK3β and its ratio to total GSK3β were significantly decreased during repeated testing **(Chapter 4)**.

Our experiments have identified the role of timing and exposure to a context in the development of behavioural and molecular changes during the modified swim test. A “premature” exposure to swimming on Day 3 instead

of Day 5 did not result in expression of GSK3β **(Chapter 4)**. On other hand, a replacement of a swim session with an exposure to the context of testing on Day 2 and Day 5 or the omission of intermediate swimming or context exposure on these days affected floating behaviour and brain GSK3β mRNA in the modified swim test **(Chapter 4)**. Together, our experiments suggested the critical role of GSK3β in the "consolidation phase" of the development depressive-like features associated with enhanced conditioning to adverse context.

Two-week delivery of low dose of imipramine (7.5 mg/kg/day), thiamine and benfotiamine (200 mg/kg/day) has precluded an increase of floating and over-expression of in mice during the last session of the modified forced swim test **(Chapter 5)**. Given that all these compounds were shown to decrease GSK3β activities, these data further suggest the role of this molecular factor in enhanced contextual conditioning associated with depressive-like state. In addition, these data have identified thiamine and its precursor as antidepressant agents and suggested their usefulness in treatment of depression in clinic **(Chapter 5)**.