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Research Number: 4220
Title: Regulation of Adult Neurogenesis in Rat Hippocampal Gyrus by Triiodothyronine (T3) Treatment
Principal Investigator: Renana Eitan
Institute: Hadassah Medical Center, Jerusalem
Duration of the funding: 6 months

Background: The thyroid hormone triiodothyronine (T3) may accelerate and augment the action of antidepressants. Antidepressants up-regulate neurogenesis in adult rodent hippocampus. Stress plays an important role in the development of affective disorders. Adverse life events influence brain development and subsequent adult behavior and play an important role in the causation of certain psychiatric disorders including depression.

Aims: (i) We studied the effect of T3 and T3+fluoxetine in enhancement of hippocampal neurogenesis beyond that induced by fluoxetine alone and the correlation with antidepressant behavior in the novelty suppressed feeding test (NSFT); (ii) We validated an animal model for depression, the chronic mild stress (CMS).

Methods: Rats were administered fluoxetine (5 mg/kg.d), T3 (50 mg/kg.d), fluoxetine (5 mg/kg.d)+T3 (50 mg/kg.d) or saline, for 21 d. Neurogenesis was studied by doublecortin (DCX) immunohistochemistry in the subgranular zone (SGZ) of the hippocampus and the subventricular zone (SVZ). In the novelty suppressed feeding test (NSFT), latency to feeding in animals deprived of food was measured. Animals assigned to the CMS groups, underwent a regimen of exposure to various types of environmental stressors for the duration of 5 weeks.

Results: Fluoxetine and fluoxetine+T3 increased the number of doublecortin-positive (DCX+) cells in the SGZ compared to saline (p=0.00005, p=0.008, respectively). There was a trend towards an increased number of DCX+ cells by T3 compared to saline (p=0.06). Combined treatment with fluoxetine+T3 further increased the number of DCX+ cells compared to T3 or fluoxetine alone (p=0.001, p=0.014, respectively). There was no effect of any of the treatments on number of DCX+ cells in the SVZ. In the NSFT, all treatments (T3, fluoxetine+T3 and fluoxetine) reduced latency to feeding compared to saline (p=0.0004, p=0.00001, p=0.00009, respectively). Fluoxetine+T3 further reduced latency to feeding compared to T3 alone (p=0.05). Using the Balb/c mice strain, no difference was found between the CMS exposed vs. CMS non-exposed mice. However, using strain Nu. NIH1291#11639 mice demonstrated a significant difference between the CMS exposed vs. CMS non-exposed mice.

Conclusions: The results suggest that enhancement of antidepressant action by T3 may be related to its effect of increasing hippocampal neurogenesis and that the antidepressant effect of these treatments is specific to the hippocampus and does not represent a general effect on cell proliferation. In this study we also validated the CMS model of depression in our lab.

Key words: depression, antidepressants, T3, neurogenesis, animal model, chronic mild stress
Publications associated with the project:
