

DIRECT MODULATION OF GABAERGIC TRANSMISSION BY THYROID HORMONES (THs) IN HIPPOCAMPUS

Gabriele Losi and Giulia Puia

Dept. Biomedical Science, University of Modena and Reggio Emilia, via Campi 287, Modena, ITALY

Thyroid hormone are critically involved in development and function of the central nervous system. THs genomic effects are mediated by specific nuclear receptors that modulate the expression of different target genes. However THs exert also a faster non genomic series of effects acting directly on membrane receptors. It was shown that T3 can accumulate in nerve terminals and be released from synaptosomes after depolarization, suggesting a role of neuromodulator. Furthermore several human nervous disorders involving GABAergic system (anxiety, depression, cognition impairment) are related to thyroid hormones imbalance.

We studied THs direct (non genomic) effect on GABA mediated inhibitory transmission in hippocampal neurons in culture and in slices. T4 and T3 reduce currents mediated by GABA_A receptors expressed in rat hippocampal cultures with similar potency (EC₅₀ 12μM). Both T4 and T3 can decrease the size (at 10 μM: -40 ± 8 % and -32 ± 5 % respectively) and number (-39 ± 14 % and -27 ± 8 %) of spontaneous inhibitory postsynaptic currents (sIPSCs) recorded in cultured hippocampal neurons. Similar results were observed in cortical neurons. In hippocampal subiculum neurons in slices T4 and T3 significantly reduced sIPSCs peak amplitude (from 45 ± 3 pA to 36 ± 3 pA with T4 20 μM and from 66 ± 10 pA to 47 ± 10 pA with T3 20 μM) and frequency of sIPSCs (from 2.86 ± 0.63 Hz to 1.57 ± 0.34 Hz with T4 20 and from 2.35 ± 0.77 Hz to 1.46 ± 0.69 Hz with T3 20). The duration of synaptic current was unaffected by THs.

GABA_A mediated inhibitory transmission has two components: a phasic current mediated by synaptic activity and a tonic current due to low extracellular GABA concentration. GABA tonic current in hippocampal slices, was reduced by T3 (at 20 μM: -51 ± 9%) but not by T4, and the same effect was observed in hippocampal cultures.

Taken together our data show that both T3 and T4 modulate GABA synaptic transmission but only T3 can reduce tonic inhibition. Considering that T3 is highly concentrated in nerve terminal, the finding that this hormone can affect both tonic and phasic GABA currents is of great relevance because of the tight correlation between THs imbalance and mental disorders.