THYROID HORMONES MODULATE GLUTAMATERGIC NEUROTRANSMISSION IN HIPPOCAMPUS

Puja Giulia, Losi Gabriele, Garzon Giorgio, Baraldi Mario

Dept. of BioMedical Sciences, University of Modena and Reggio Emilia, Via G. Campi 287, 41100 Modena, ITALY. Author for correspondence: Puja Giulia, tel +39-059-2055135; fax +39-059-2055376; e-mail: puja@unimore.it

Tyroid hormones (THs) such as L-T3 and L-T4 are essential for maturation and function of Central Nervous System (1). THs deficiency indeed is known to profoundly affect such cognitive functions as learning and memory which are know to depend on the structural and functional integrity of the hippocampal formation (2).
The classical mechanism of L-T3 is genomic however a number of recent reports showed that several of its effects are achieved through non genomic pathways (3) as for example through modulation of plasma membrane receptors (4).
Glutamate plays an important role in cognitive processes and after been released from the presynaptic terminal activates ionotropic and metabotropic receptors.
The aim of this study was to analyze the modulatory effects of THs on glutamatergic neurotransmission mediated by native ionotropic receptors either in hippocampal neurons in primary cultures or in acutely dissociated slices and on recombinant receptors expressed in fibroblasts.
By employing the patch clamp technique in the whole cell configuration we investigated THs effect on currents mediated by glutamate receptors (NMDAR and AMPAR).
In hippocampal cultures L-T4 and L-T3 inhibited NMDA- evoked currents with similar potencies ($IC_{50}T4$=8±3 μM, $IC_{50}T3$= 15±7 μM). The antagonism was not competitive for glutamate or glycine binding sites and was voltage independent. Reverse T3 (rT3), an endogenous metabolite of T3 devoid of genomic activity, also decreased NMDAR function even though at higher concentrations.
L-T3 (10 μM) reduced NMDA-evoked current in fibroblasts expressing NR1a-NR2A or NR1a-NR2B in the same fashion (39 ± 9 % for NR2A and 46 ± 3 % for NR2B).
We also tested the THs modulation of AMPAR-mediated currents: L-T3 (30 μM) significantly reduced KA- evoked current (- 41±8 %) while the same concentration of L-T4 was ineffective.
In hippocampal slices the frequency of miniature excitatory postsynaptic currents (mEPSCs) was reduced by L-T3 (from 0.17± 0.03 Hz to 0.09±0.02 Hz, n=15 $p<0.01$ Student T-test), while no effect was detected on peak amplitude or decay.
In neurotoxicity experiments we found that L-T3 reduced glutamate and NMDA- induced neuronal death but only at high concentrations.
Taken together our data show for the first time that THs can regulate excitability in hippocampal neurons by directly modulating glutamatergic receptor function and provide a novel explanation for the origin of various neurological symptoms related to thyroid dysfunction.

References:

(1) Bernal J. (2002) *J. Endocrinol . Investig.* 25:268-288; (2) Gilbert M.E. *Dev. Brain Res.* (2004) 148: 11-18; (3) Davis PJ et al. *Tyroid*: 6(5): 497-504 (1996); (4) Wiens S.C and Trudeau V.L.(2006) *Comp Bioch. And Physiol*. 144(3):332-44.