THYROID HORMONE METABOLITES, INCLUDING 3-IODOTHYRONAMINE (T1AM) AND 3-IODOTHYROACETIC ACID (TA1) ARE ENDOWED OF NEUROPROTECTIVE EFFECTS

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Introduction: Thyroid hormone is essential for neuron development and for brain post-natal plasticity. Recent evidence indicate that thyroid hormone metabolites, including the 3-iodothyroacetic acid (TA1) may also modulate neuron plasticity in rodents including stimulation of learning and memory consolidation with a mechanism dependent on the activation of the histaminergic system (Musilli et al., 2014). In order to compare the effects of thyroid hormone with that of TA1, we aimed to investigate whether TA1was able to reduce pharmacologically-induced neuron hyperexcitability and whether TA1and other thyroid hormone metabolites, including 3-iodothyronamine (T1AM), thyronamine (T0AM), thyroacetic acid (TA0) and 3,5,3'-triiodothyroacetic acid (TRIAC) were also endowed of neuroprotective effects against excitotoxic damage in organotypic hippocampal slices.

Materials and methods: CD1male mice were treated intraperitoneally with saline solution or TA1(4, 7, 11, or 33μg/kg) before receiving 90mg/kg pentylenetrazole subcutaneously. The following parameters were measured: latency to first seizure onset, number of mice experiencing seizures, hippocampal levels of c-fos, and PI3K/AKT activation levels. Organotypic hippocampal slices were exposed to vehicle or to 5μM kainic acid (KA) in the absence or presence of TA1, T3, 3,5,3'-triiodothyroacetic acid (TRIAC), T1AM, thyronamine (T0AM), or thyroacetic acid (TA0). Neuronal cell death was measured fluorimetically. The ability of TA1and T3, TRIAC, T1AM, T0A, and TA0 to activate the PI3K/AKT cascade was evaluated by Western blot. The effect of TA1on KA-induced currents in CA3neurons was evaluated by patch clamp recordings on acute hippocampal slices.

Results: TA1(7and 11μg/kg) significantly reduced the number of mice showing convulsions and increased their latency of onset, restored pentylenetrazole-induced reduction of hippocampal c-fos levels, activated the PI3K/AKT, and reduced GSK-3β activity. In rat organotypic hippocampal slices, TA1reduced KA-induced cell death by activating the PI3K/AKT cascade and increasing GSK-3β phosphorylation levels. Protection against KA toxicity was also exerted by T3and other T3metabolites studied. TA1did not interact at KA receptors. Both the anticonvulsant and neuroprotective effects of TA1were abolished by pretreating mice or organotypic hippocampal slices with pyrilamine, an histamine type 1receptor antagonist (10mg/kg or 1μM, respectively).

Conclusions: TA1exerts anticonvulsant activity and is neuroprotective *in vivo* and in vitro. These findings extend the current knowledge on the pharmacological profile of TA1and indicate possible novel clinical use for this T3metabolite.