Neuroprotective effects of 3-iodothyroacetic acid (TA1), a by end product of thyroid hormone metabolism: evidence for histamine involvement

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3-iodothyroacetic (TA1) is among the end metabolites of thyroid hormone. We recently demonstrated that TA1 pharmacological effects, including stimulation of learning, hyperalgesia and itch, involve the histaminergic system effects (Musilli et. al 2014, Laurino et. al 2015a, Laurino et al 2015b).
Experimental evidence suggest histamine might have neuroprotective effects which could include the control of neuronal epilettogenic activity. Accordingly, post-ischaemic histamine administration and prolonged release of histamine in response to brain ischemic insults reduced neuronal damage. Histamine role in seizures was found instead controversial since facilitatory as well as protective effects of histamine on convulsions and seizures were reported (Kiviranta et al., 1995; Chen et al., 2003; reviewed by Adachi, 2005).
We aimed to investigate whether TA1 protected in an *in-vitro* and *in-vivo* model of epilepsy and neuronal damage and the signaling pathway activated. To this aim, rat organotypic hippocampal slices were prepared as described by Gerace et. al (2012) and exposed to kainic acid 5 mM for 24 h with or without TA1 (100 nM-10 μM) in the absence or in the presence of pyrilamine (1 μM). Cell toxicity was evaluated by propidium iodide (PI) fluorescence.
In another set of experiments, CD1 mice were treated i.p. with saline or TA1 (4, 11, 33 μg/kg) and after 15 min with PTZ (s.c.; 70 mg/kg). Mice were observed for clonic seizure activity, defined as clonus of the whole body lasting over 3 s with an accompanying loss of righting reflex, for 20 minutes (?wi?der et al 2016). After 24 h from PTZ administration mice were sacrificed and hippocampus and neocortex were collected for western blot analysis.
TA1 (10 μM) significantly reduced the damage induced by Kainic acid in the CA3 region. This reduction was abolished by pyrilamine. While PTZ caused clonic seizures in the 100% of animals, in those pretreated with TA1 (11 μg/kg), clonic seizure incidence was reduced to 60% and the latency of seizure occurrence was delayed. In hippocampi of mice pretreated with TA1 (11 μg/kg), an increase in pmTOR and pAKT levels and a decrease in pGSK3b compared to those receiving only PTZ, was observed. Mice received TA1 (1.32, 4 , 11 μg/kg) remained on the accelerated rota-road showing incidence of falls not different from those measured in saline-treated mice.
These data suggest that TA1, by activating mTOR and AKT signaling cascade, induced neuroprotection in an in vitro and in vivo model of epilepsy likely involving (interacting with) the histaminergic system.

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