Central effects induced by systemic pharmacological administration of 3-iodothyroacetic acid (TA1), an endogenous derivative of Thyroid Hormone.

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We recently reported 3-iodothyroacetic acid (TA1), a by-product of thyroid hormone metabolism suspected to mediate non genomic effects of thyroid hormone, acutely stimulated learning and produced hyperalgesia in mice activating the histaminergic system (Musilli et al., 2014; Laurino et al., 2015a; 2015b). It is well known that thyroid and histaminergic system dysfunctions associated with alteration of mood, disturbances of the circadian clock and increased susceptibility to seizures (Song et. al., 2010; Bhowmik et al., 2012). We now aim to investigate whether TA1 systemically injected to mice induced increase of attention, of vigilance and whether TA1 was endowed of antiepileptic effects.

CD1 male mice received i.p. TA1 (1.32, 4 and 11 µgkg-1) or saline and, after 15 min, spontaneous locomotor activity and motor coordination were evaluated by the hole board and the rota-road test respectively. TA1 (1.32, 4 and 11 µgkg-1 i.p.) effect on mice vigilance was assessed by the forced swim test and measuring the sleeping time and the latency of sleep onset in mice receiving an acute ipnotic dose of ethanol (3.5 mgkg-1; i.p.). TA1 effect on epilepsy was evaluated in in vivo (mice treated with 90 mgkg-1 pentylenetrazole s.c. (scPTZ) or in in vitro models (organotypic hippocampal slices exposed for 24 h to 5 □M kainate; KA). The latency of seizure onset and the number of convulsant mice were measured whereas KA toxicity in the CA3 region was evaluated by propidium iodide (PI) fluorescence. KA-induced current in CA3 neurons was evaluated electrophysiologically. Hippocampal and hypothalamic signals activated by 4 or 7 □gkg-1 TA1 were measured by Western blot. Experiments were repeated in mice pre-treated with pyrilamine (10 mgkg-1) or zolantidine (5 mgkg-1) or immepip (10 mgkg-1).

TA1 (4 and 11 □gkg-1; i.p.) increased mice spontaneous locomotor activity, reduced the immobility time in the forced swim test without giving motor incoordination, effects reverted by zolantidine and pyrilamine respectively. TA1 (4 □gkg-1) significantly delayed the onset and shortened the duration of ethanol-induced sleep. At the same dose TA1 increased hypothalamic p-mTOR and p-GSK-3β levels, effects prevented by immepip pre-treatment. TA1 (7 and 11 □gkg-1) significantly reduced ($P<0.05$ and $P<0.01$ vs. vehicle) the number of convulsant mice (13/20 and 14/22 respectively vs 18/18 of vehicle) and increased seizure latency. 7 □gkg-1 TA1 activated PI3K/AKT/GSK-3β signaling cascade in mice hippocampus and restored c-fos levels reduced by scPTZ. 10 □M TA1 reduced KA toxicity (-30 %), by activating the PI3K/AKT/GSK-3β cascade indicating a neuroprotective effect of the acid. TA1 did not modify KA-induced current in CA3 hyppocampal neurons. Both anticonvulsant and neuroprotective effects were abolished by PYR.

TA1 confirms its outstanding pharmacological profile now including stimulation of attention, vigilance and protective effects in epilepsy. Even if the mechanism(s) responsible for such effects

remain elusive yet we have identified the hypothalamic and the hippocampal PI3K/AKT/GSK-3β cascade and the involvement of the histaminergic system activation. To note the PI3K/AKT/GSK-3β cascade is the same one activated by known anticonvulsant drugs including histamine type 3 receptor antagonist/inverse agonists which are currently investigating for their potential effectiveness in epilepsy and its devastating brain consequenecs including memory dysfunction and depression.

Musilli et al. (2014) Br J Pharmacol 171: 3476–3484

Laurino et al. (2015a) Eur J Pharmacol 761: 130-4

Laurino et al. (2015b) Br J Pharmacol 172:1859-68.

Song et al. (2010) Thyroid 20: 955-958

Bhowmik et al. (2012)Br J Pharmacol 167: 1398-1414