

Alkaline phosphatase multi-tasks in the brain

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Caroline Fonta¹, Marie Gleizes¹, Anne Briolay², Thomas Cruz³, David Magne², Stéphane Balayssac³, Jose-Luis Millan⁶, Lionel G Nowak¹, Myriam Malet-Martino³, Véronique Gilard³, David Magne² Constitutionnelle, Centre Hospitalier de Versailles, Le Chesnay, France; ⁶ Sanford Children's Health Center, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, USA

INTRODUCTION:

There are several genes for alkaline phosphatase (AP). One of them codes for TNAP (Tissue Non-specific Alkaline Phosphatase). It is a ubiquitous ectoenzyme located in different tissues in the body. In the brain, this enzyme is GPI anchored on the neuronal membrane, especially on node of Ranvier and synapses (Fonta et al., 2005). Mutations of the TNAP gene are responsible for hypophosphatasia, a rare disease characterized by defective bone mineralization (Millan, 2006) caused by pyrophosphate accumulation. In the severe form, hypophosphatasia is associated with epileptic seizures (Whyte, 1995). This neurological disorder could be explained by a decrease in GABA level due to lack of pyridoxal 5'phosphate (PLP) dephosphorylation.



> AP in the brain is involved in **neuronal inhibition** via GABA and adenosine production as well as in **neurite maturation**. Besides AP may play a role in inflammation regulation via proinflammatory cytokines, cystathionine metabolism and nucleotide hydrolysis.

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Results 39 metabolites identified in whole brain extract 8 metabolites significantly impacted by TNAP gene invalidation. Akp2 (+/-) / (+/+) mice have very similar metabolomes. Very large changes in Knockout mice for GABA, cystathionine and adenosine concentration compared to Akp2 (+/+) and Akp2 (+/-). If ratio<1 metabolite concentration decreased If ratio>1 metabolite concentration increased. Bars encompass to the 95% confidence interval of the ratio. Colored symbols indicate significant variations between different mice Ratio of the means (± 95% CI) 3 metabolites strongly impacted by TNAP gene invalidation 2000cells/cm² DMEM medium _____ 1000 200 10 Amount (nmol/g) Concentration decreased by 40 % Concentration increased by 450 % Concentration decreased by 80% ATP → ADP Homocysteine -Glutamine Serine Glutamate Neuronal Cystathionine + H2C transmission → GAD 🧲 PLP — GABA Neuronal inhibitior that the metabolome of > PLP dephosphorylation by TNAP is required for cystathionine and GABA \geq In parallel with its regulatory role in neuronal synaptic transmission, TNAP could be involved in inflammation. SK-N-SH 2000cells /cm² DMEM medium PLP - (-) Inflammation — IL1β / TNFa PLP (+)/ l (-) PLP dependent — Cystathionine enzymes ATP



Inactivation of the TNAP gene in mice (Akp2) produces an animal model of severe hypophosphatasia with bone mineralization defects and epileptic seizures (Waymire et al. 1995, Narisawa et al. 1997). These mice usually die before too weeks of age.

We use two approaches to understand the function of TNAP in the brain : * Metabolomic research in order to determine new TNAP substrates and products that are directly or indirectly affected by TNAP, using mice invalidated for TNAP gene.

* Neuronal cell culture to study the effect of blocking TNAP activity on cell proliferation and differentiation.



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