

Role of PI3K Overactivation in Dendritic Spines Plasticity

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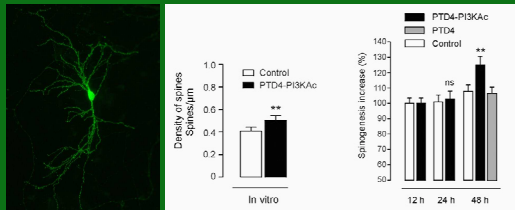
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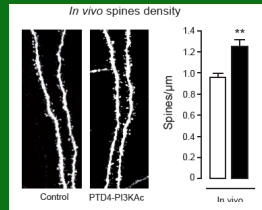
Overactivation of PI3K increases synapse density and spinogenesis in *Drosophila* and mammals (Martin-Peña et al., 2006; Cuesto et al., 2011). Using the transduction peptide, PTD4-PI3KAc, to produce a controlled overactivation of PI3K, we have demonstrated that hippocampal cultured neurons increase a 26 % in spine density; while *in vivo* effects in the hippocampus of adult rats after 72 hours treatment, lead to an increase of 30%. After 96 hours of treatment, this spinogenic effect is reduced to 13%. Animals treated with the peptide, exhibit enhanced cognitive behavior measured by a fear conditioning assay (CFC). CFC per se, induces an augment of 30% in dendritic spines; although no differences in spine number were found between controls and PI3K injected animals. Experimental conditions employed were: naïve (Controls and PI3K injected rats) at 72 and 96 hours, CFC animals (Controls and PI3K injected). Spines density and morphology, were analyzed in all conditions. Characterization of spine morphology suggests that, *in vivo*, PI3K activation mainly leads to the formation of thin spines, having significantly smaller head areas. Thin spines are highly motile and dynamic, thus principally related with learning processes. Small spines are also NMDA receptor dominated, thus, we have studied changes in structural genes related to synaptic transmission (GluR1, 2, 3) as well as to synaptic plasticity (NR1, NR2). Loss of synaptic contacts is a major feature in neurodegenerative processes, such as in Alzheimer's disease. Our data imply that PI3K or the pharmacological target of PI3K, may be used in a future treatment of neurodegenerative diseases.

1. PI3K: SYNAPTOGENIC AND SPINOGENIC EFFECT

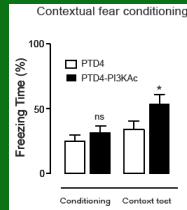
Spines density increases *in vitro*



Spines density increases *in vivo* (72 H)

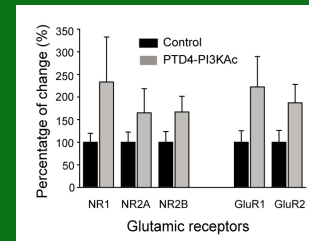


Enhanced cognitive behavior (injection in lateral ventricle)

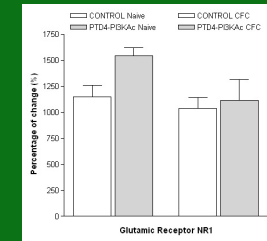


3. CHANGES IN GLUTAMIC RECEPTORS *in vitro* and *in vivo*

in vitro

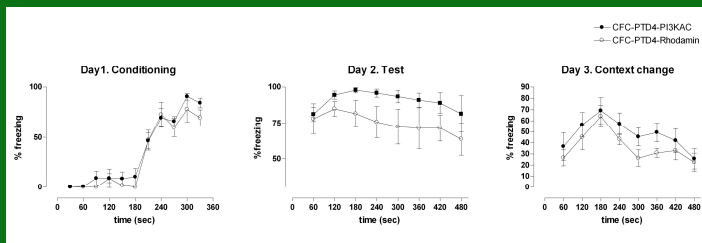


in vivo

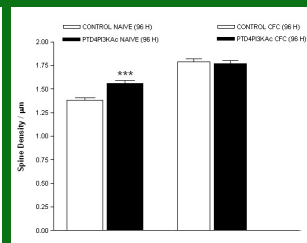


2. PI3K AND A CONTEXTUAL FEAR CONDITIONING ASSAY INDUCE SPINOGENESIS

Enhanced cognitive behavior (injection in the hippocampo (CA1))

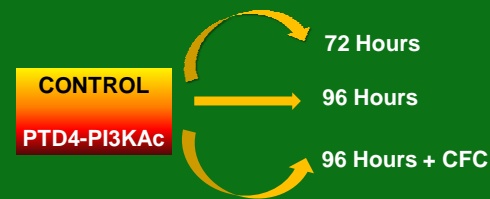


Spines Density (96 H)



4. PI3K OVERACTIVATION AND CFC LEAD TO CHANGES IN SPINE MORPHOLOGY

TEMPORAL PROFILE OF SPINE MORPHOLOGY



HEAD AREA: TEMPORAL PROFILE

