

# Tonic activation of VPAC<sub>1</sub> receptors by VIP modulates theta-burst induced LTP in the hippocampus: transduction pathways and GABAergic mechanisms.

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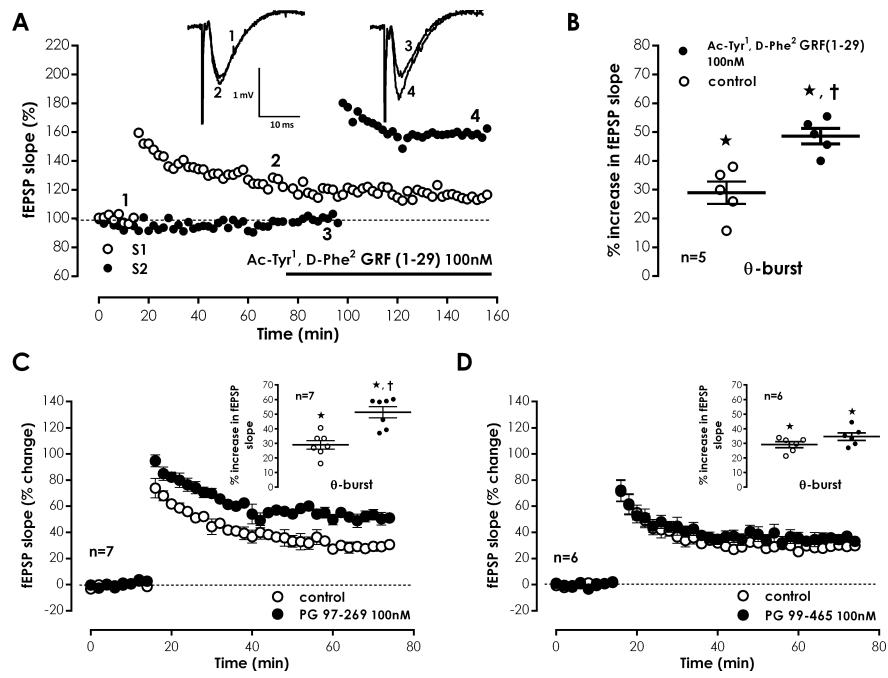
April 8, 2021

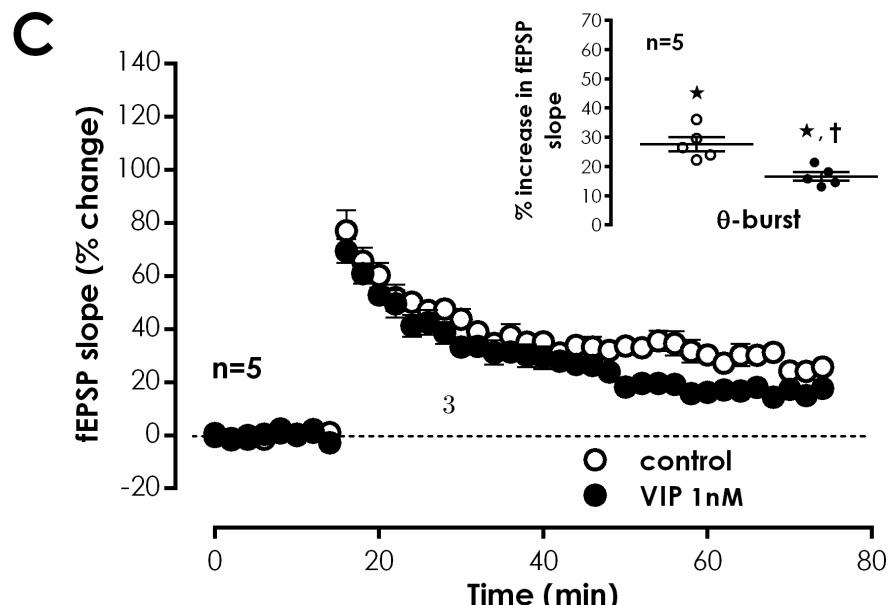
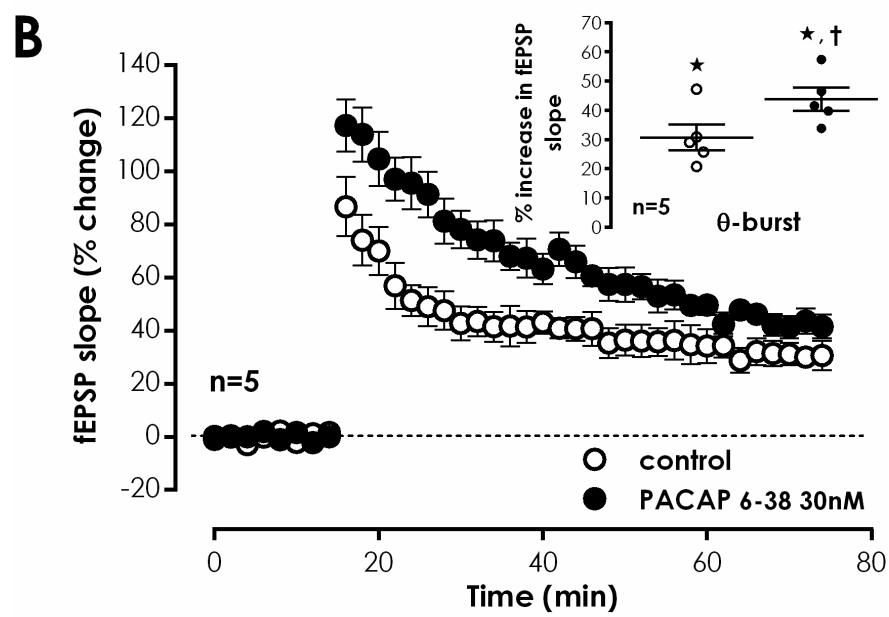
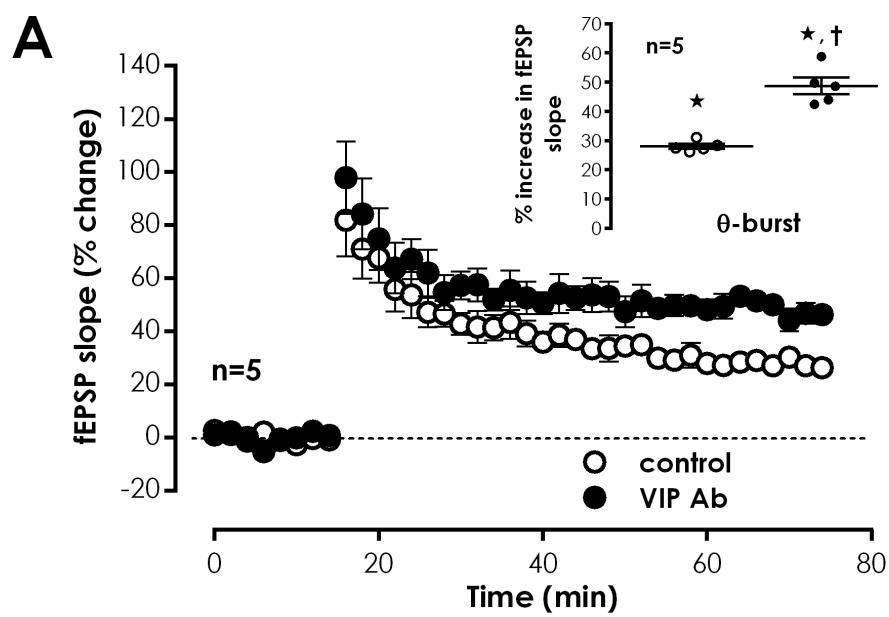
## Abstract

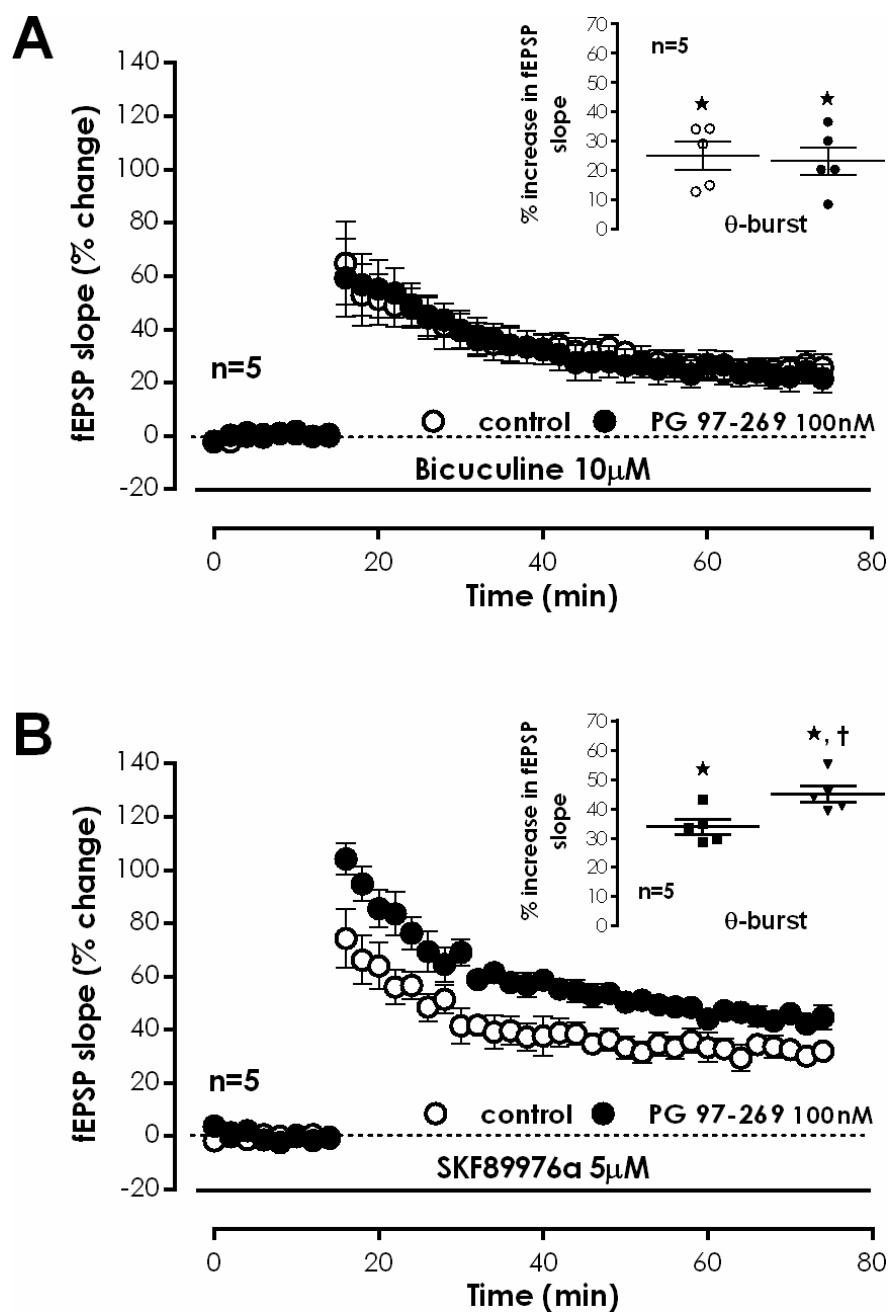
Background and purpose Vasoactive intestinal peptide (VIP), acting on both VPAC<sub>1</sub> and VPAC<sub>2</sub> receptors, is a key modulator of hippocampal synaptic transmission, pyramidal cell excitability and synaptic plasticity phenomena, like long-term depression (LTD), partly through modulation GABAergic disinhibitory circuits. VIP effects on LTP and the involvement of disinhibition were scarcely investigated. Experimental approach The influence of endogenous VIP on CA1 LTP induced by TBS was evaluated in the CA1 area of hippocampal slices using field-excitatory electrophysiological recordings from young-adult Wistar rats using selective VPAC<sub>1</sub> and VPAC<sub>2</sub> antagonists. Phosphorylation of GluA1 AMPA receptor subunits and Kv4.2 potassium channels was evaluated in hippocampal membranes obtained from such slices by Western blot. Key results Here we show that VIP, acting on VPAC<sub>1</sub> (but not VPAC<sub>2</sub>) receptors, is an endogenous inhibitor of hippocampal LTP induced by theta-burst stimulation (TBS) in the CA1 area of the hippocampus of young adult Wistar rats. This effect is dependent on GABAergic transmission and relies on the integrity of NMDA and CaMKII-dependent LTP expression mechanisms but not on PKA and PKC activity. Furthermore, it regulates the expression and Ser<sub>438</sub>phosphorylation of Kv4.2 potassium channels responsible for the A-current while inhibiting phosphorylation of Kv4.2 on Thr<sub>607</sub>. Conclusions and implications Altogether this suggests that endogenous VIP controls the expression of hippocampal CA1 LTP by regulating disinhibition through activation of VPAC<sub>1</sub> receptors in interneurons. This may impact the expression and phosphorylation of Kv4.2 K<sup>+</sup> channels at hippocampal pyramidal cell dendrites.

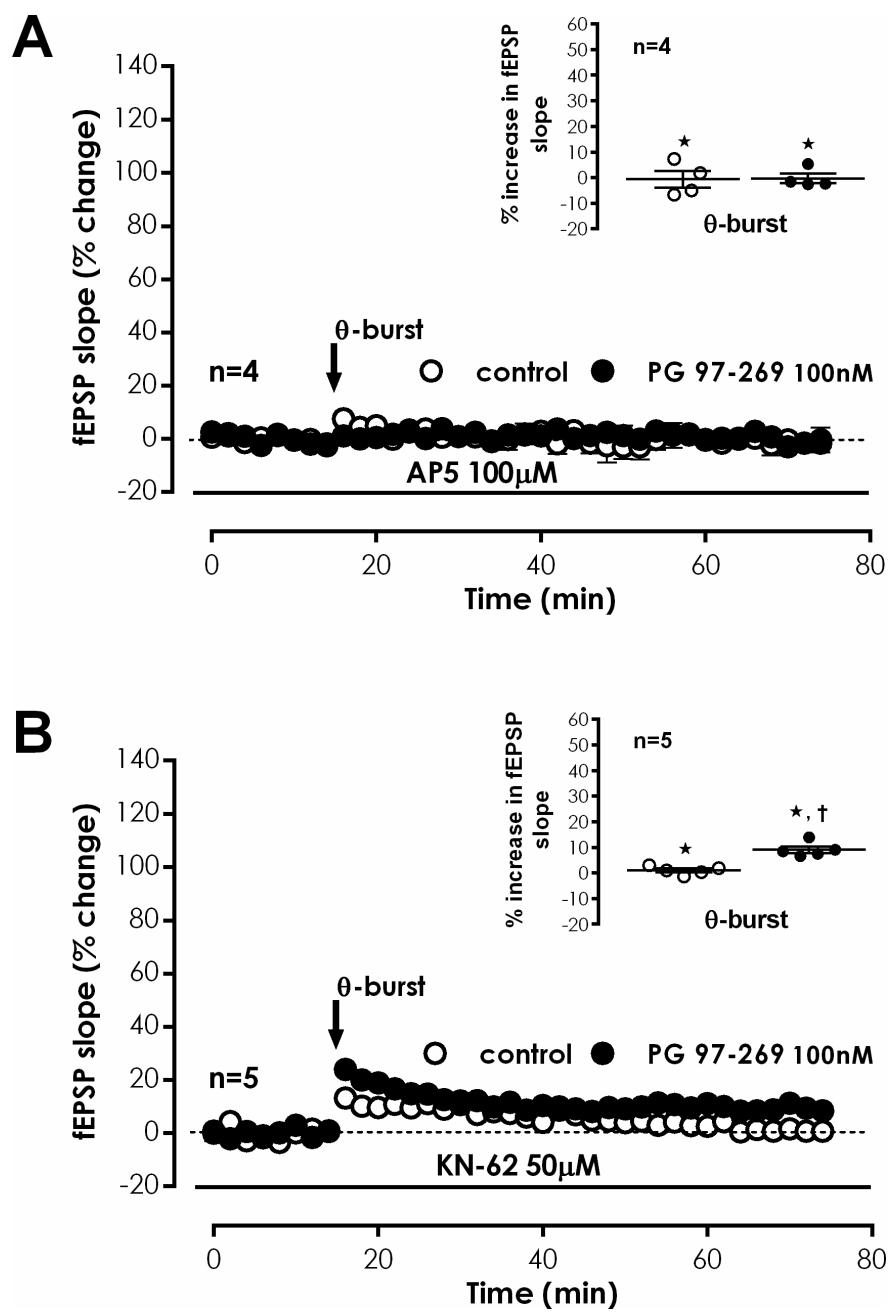
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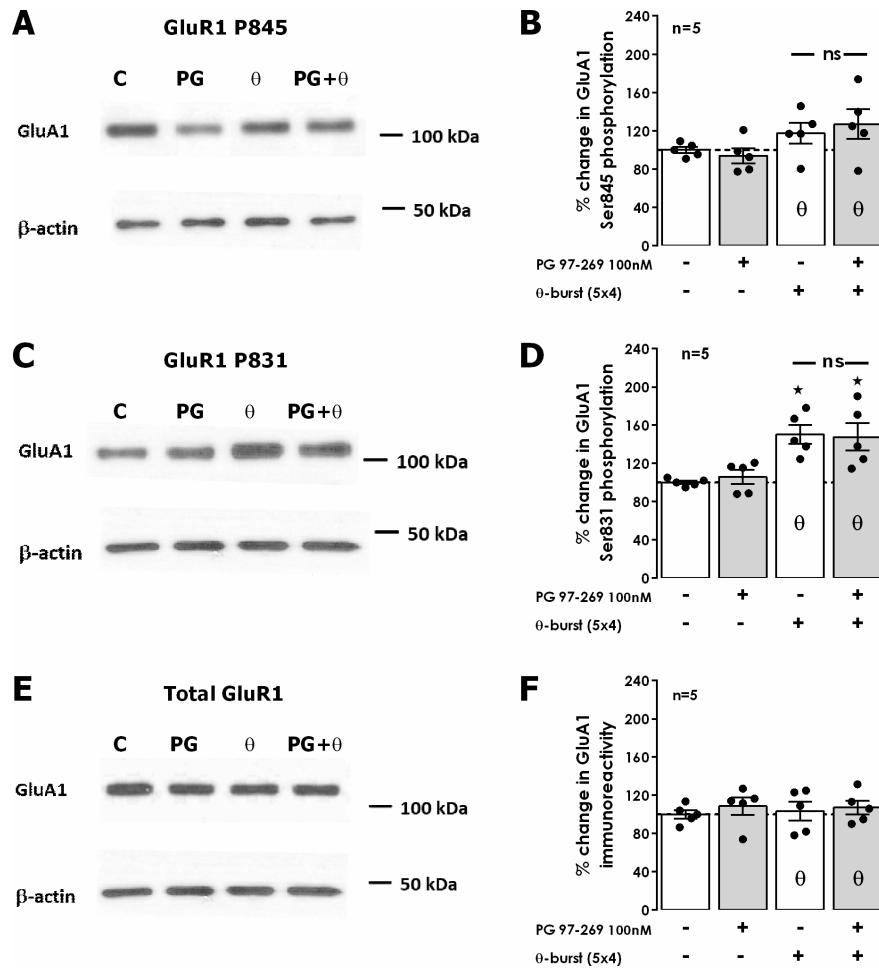
Cunha-Reis 2021 VIP LTP Br J Pharm vfinal.pdf available at <https://authorea.com/users/406578/articles/517176-tonic-activation-of-vpac1-receptors-by-vip-modulates-theta-burst-induced-ltp-in-the-hippocampus-transduction-pathways-and-gabaergic-mechanisms>

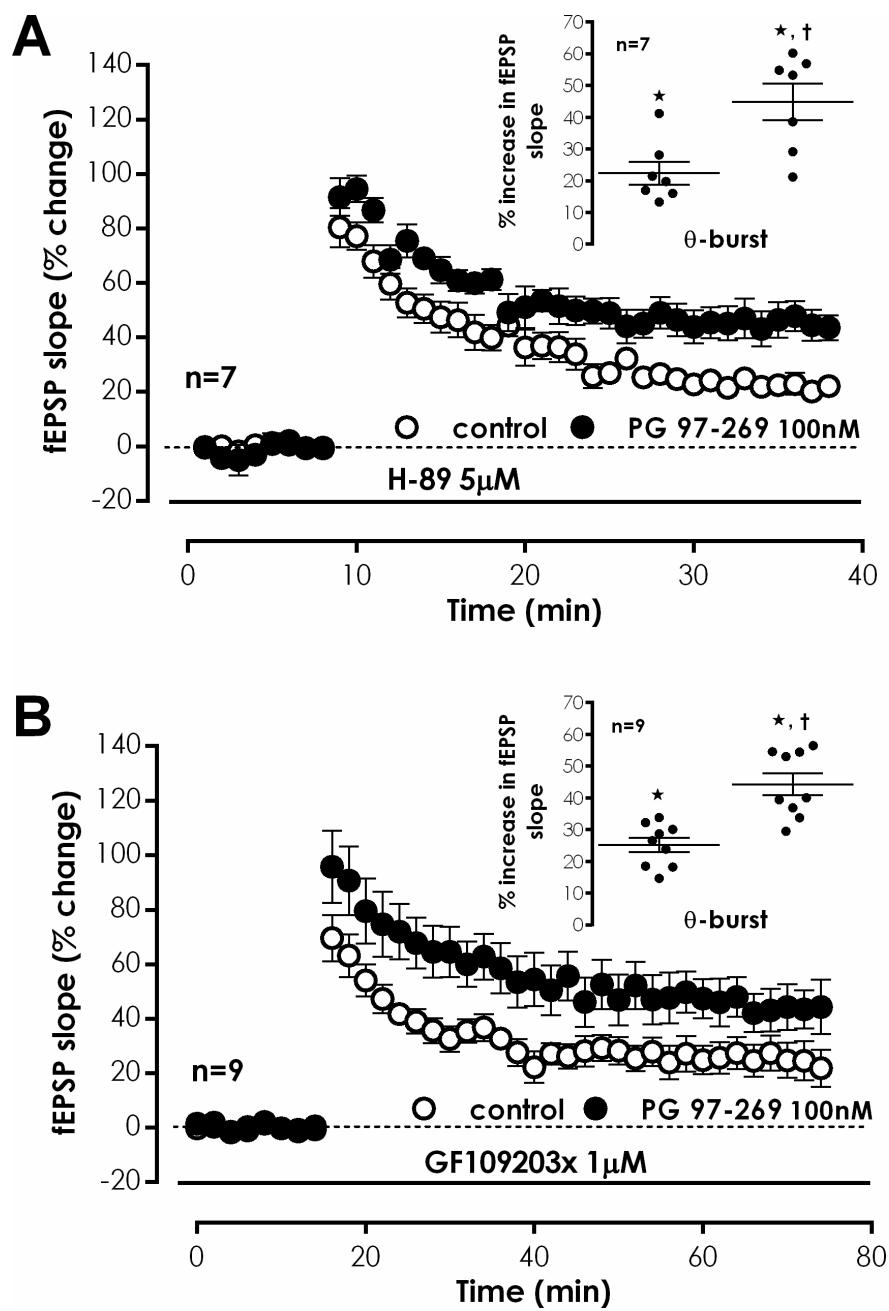


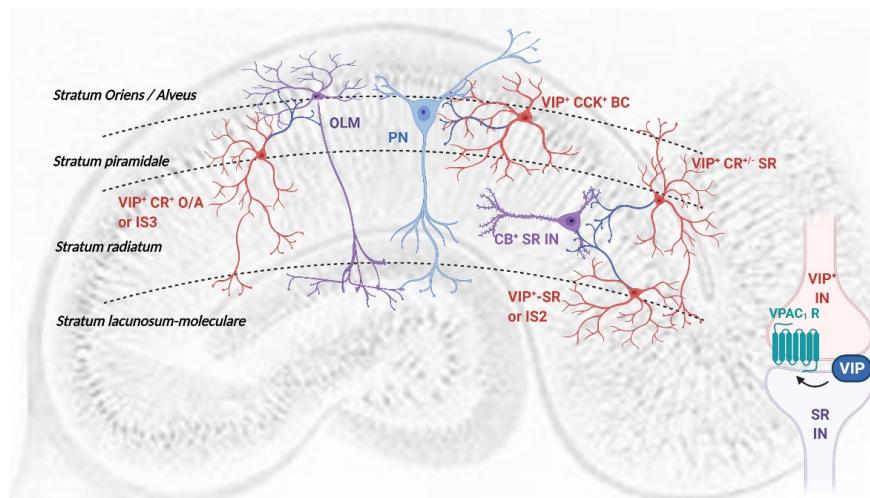
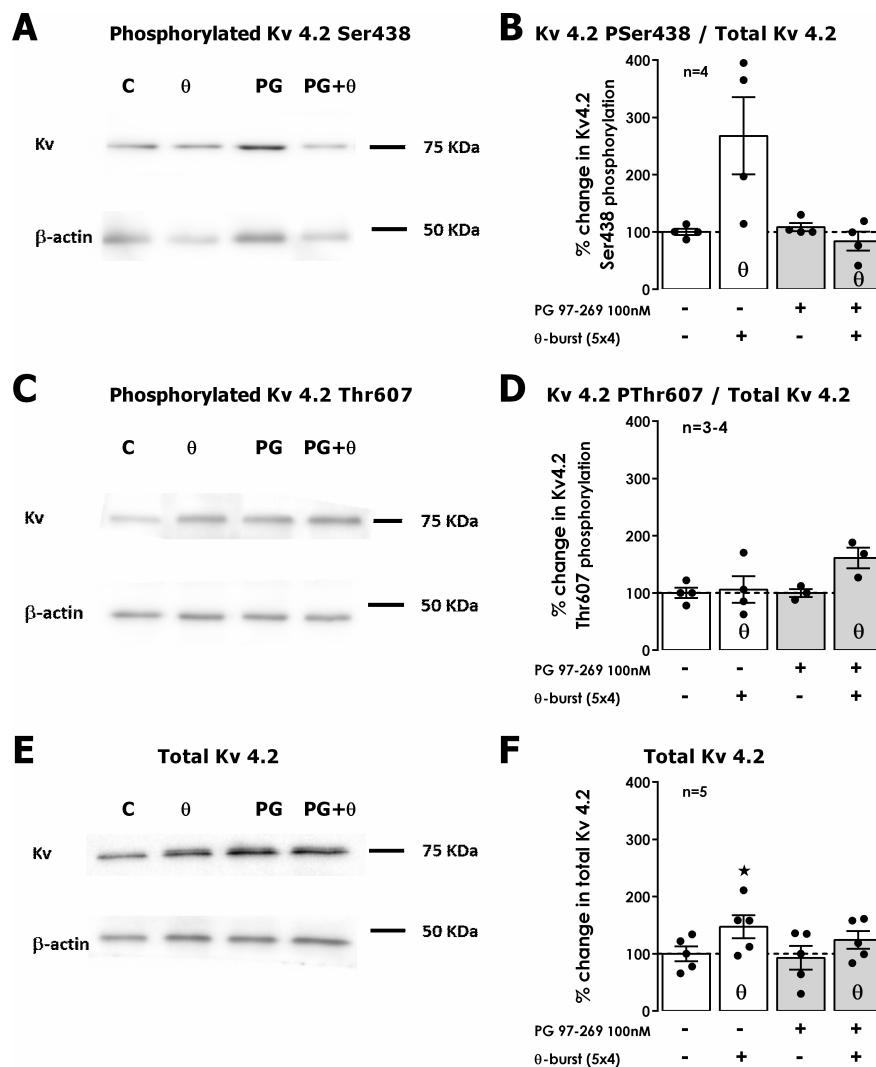












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Table 1 - BRJPharmacol 2021v2.pdf available at <https://authorea.com/users/406578/articles/517176-tonic-activation-of-vpac1-receptors-by-vip-modulates-theta-burst-induced-ltp-in-the-hippocampus-transduction-pathways-and-gabaergic-mechanisms>