A role for astrocytes in modulation of GABAergic transmission and synaptic plasticity by VIP?

Place of work/: Epilepsy and Aging Team, BioISI – GER, FCUL.

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GABA is the main inhibitory neurotransmitter in the mammalian brain where it plays an important role in regulating brain activity states and preventing excessive neuronal excitation. Synaptic plasticity events are cellular mechanisms that play a crucial role in learning and memory formation. Vasoactive intestinal peptide (VIP), acting on $VPAC_1$ receptors, is released during synaptic plasticity induction and influences hippocampal synaptic plasticity through modulation of GABAergic transmission(*1*, *2*). VIP is present only in a few populations of GABAergic interneurons and regulates GABA release through activation of $VPAC_1$ and $VPAC_2$ receptors(*3*). Astrocytes are another important cellular component of GABAergic synapses and can greatly influence synaptic GABA availability. In addition, astrocytes can be activated by synaptic GABA, that enhances intracellular Ca^{2+} through several signaling pathways. This may in turn trigger the release of gliotransmitters that can influence LTP(*4*). Gliotransmitters released from astrocytes, including neuropeptides, have been described to modulate LTP induction and expression(*5*). Astrocytes express both $VPAC_1$ and $VPAC_2$ VIP-selective receptors(*6*) but their role in VIP modulation of GABAergic transmission and synaptic GABA availability was never investigated. Likewise, the influence of these receptors in astroglial responses to GABA stimuli was never studied.

This project aims to use hippocampal astrocyte cultures and hippocampal slices to investigate: 1) The influence of $VPAC_1$ and $VPAC_2$ receptors on astroglial GABA uptake; 2) The astrocytic Ca^{2+} responses to transient GABA stimuli, as would occur at GABAergic synapses during synaptic plasticity; 3) the presence of VIP, $VPAC_1$ and $VPAC_2$ receptors in astrocyte cultures as accessed by immunocytochemistry.

The influence of $VPAC_1$ and $VPAC_2$ receptors on astroglial GABA uptake kinetics mediated by GAT-1 and GAT-3 receptors will be studied as previously described(*7*), using selective agonists and antagonists for these receptors. Astrocytic Ca^{2+} responses to transient GABA stimuli will be monitored using the Ca^{2+}-sensitive fluorescent dye fura-2 acetoxymethyl ester (fura-2 AM)(*8*). VIP, $VPAC_1$ and $VPAC_2$ receptors will be detected in hippocampal astrocyte cultures by immunocytochemistry with specific antibodies. Experimental work will be conducted with the support of the BioISI cell culture and FCUL microscopy facilities.

References:

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Alternative topics: (please contact the supervisor)**:**

- Investigating the alterations in synaptic lipid rafts using atomic force microscopy and immunogold staining.
- Synaptic plasticity in the hippocampus during post weaning development and aging: influence of phosphorylation of synaptic enzymes and channels.