Vesicular glutamate transporters in normal and pathological brain

BIOLOGIE & SANTÉ 2011

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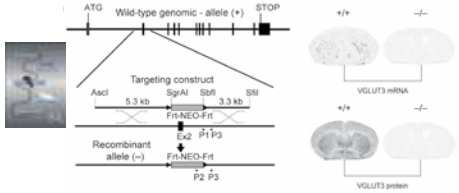
Context and objectives

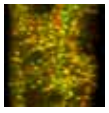
Before its exocytotic release, glutamate is accumulated into synaptic vesicles by transporters (named VGLUT1-3). These transporters are key anatomical and functional markers of glutamatergic transmission.

Our objectives were to i) investigate VGLUTs in the normal and pathological brain both in rodent and human and ii) to develop new pharmacological tools targeting the VGLUTs.

1. Mice model: **VGLUT3 knock out (VGLUT3$^{-/-}$)**

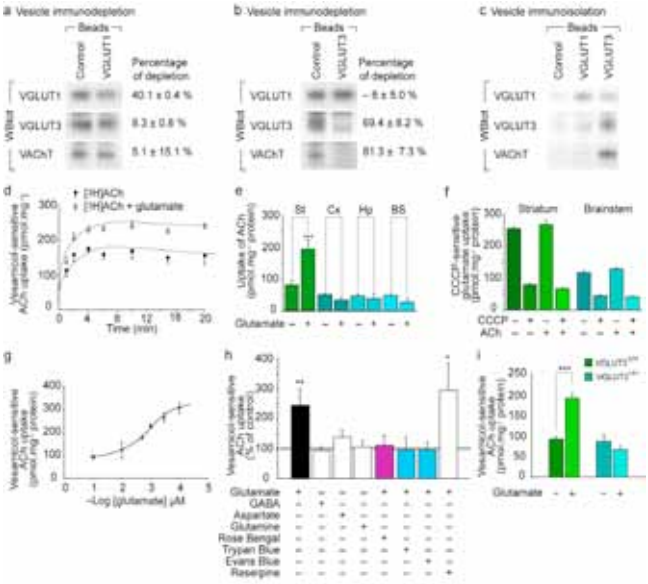


VGLUT3 stimulates vesicular acetylcholine uptake: Vesicular Synergie (VS)

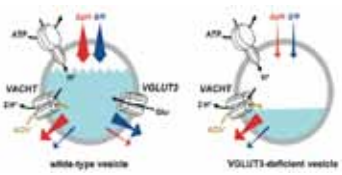


VGLUT3 + **VAChT**
In the striatum, VGLUT3 and VAChT are present in the same terminals

In striatal cholinergic terminal, VGLUT3 and VAChT are present on the same vesicles



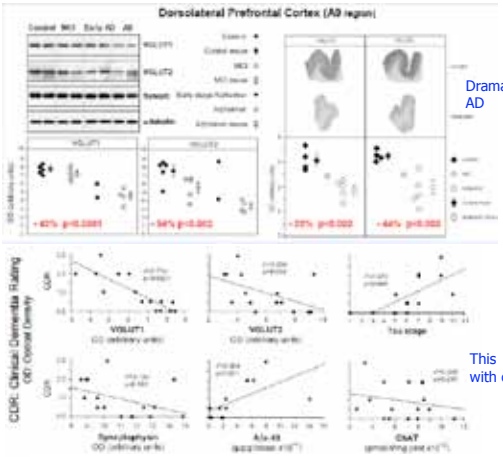
A new presynaptic regulatory mechanism: vesicular synergy



VGLUT3 stimulates acetylcholine vesicular uptake in the striatum and, thereby, positively modulates local cholinergic transmission. These data unravel a novel and unforeseen regulatory mechanism **vesicular synergy (SV)**.
SV could be influencial in various pathologies such as Parkinson disease, addiction, anxiety or depression.

Ref: Gras et al., 2008, Nat Neurosci; Amilhon et al., 2010, J Neurosci

Human Neuropathologies: Alzheimer disease (AD)

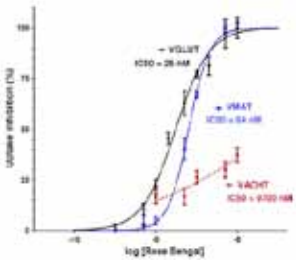


Dramatic decrease of VGLUT1&2 in AD

This decrease is highly correlated with cognitive decline

Ref: Kashani et al., 2008, Neurobiol of Aging

Neuropharmacology



Using a newly developed miniaturized assay we look for new and more specific pharmacological agents to target the VGLUTs both in vivo and in vitro. We have already established that the so called VGLUTs inhibitor Rose Bengal was in fact not specific of this class of transporter but could bind/inhibit other vesicular carriers such as the vesicular monoamine transporter (VMAT) or the vesicular acetylcholine transporter (VAChT).
We are currently analyzing new classes of high affinity, specific, VGLUTs inhibitors

Ref: Pietrancosta et al., 2010, Bioorganic and Medicinal Chemistry

Conclusion

Thanks to the ANR financial support we have fulfilled our goals and produced major results along the above described 3 axes of our work program. In addition, these results have been published in high ranking international journals.

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