Vescicular glutamate transporters as molecular regulators of neural communication (SYNVGLUT)

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Title of project or programme

Vescicular glutamate transporters as molecular regulators of neural communication (SYNVGLUT)

Principal Investigators of project/programme grant

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Source of funding information

European Research Council

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2410000

Start date of award

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Total duration of award in months

60

The project/programme is most relevant to

- Parkinson’s disease

Keywords

Research abstract in English

This proposal describes experiments aimed at defining the multiple roles of vesicular glutamate transporters (VGLUTs) in central synapses. Classically, VGLUTs transport glutamate from the cytoplasm into synaptic vesicles. Deletion of these genes disrupts synaptic glutamate release and their expression suffices to determine neurons as glutamatergic. We recently discovered that VGLUTs control additional key parameters such as quantal size and vesicular release probability, suggesting that they are fundamental regulators of synaptic strength and synaptic plasticity. To study these novel functions, we will first address whether the number of VGLUTs per vesicle (VGLUT content) can affect the amount of stored glutamate and in addition, the probability of vesicle release.

We will subsequently explore the underlying mechanisms. Second, we will test the hypothesis that different VGLUT paralogs contribute to functional differences in discrete synapse populations, as implied by our preliminary data and the distribution pattern of the two main paralogs VGLUT1 and VGLUT2 in the brain. Subsequently, we will perform structure function studies on VGLUTs in native synapses to identify the underlying molecular interactions. Finally, the little understood VGLUT3 paralog is expressed mainly in subclasses of cholinergic, dopaminergic and GABAergic neurons, but no evidence exists that demonstrates VGLUT3 s role in glutamate release. We will address whether VGLUT3 is used to co-release glutamate with other neurotransmitters, and will test whether presence of glutamate in synaptic vesicles interferes with the storage or release of other neurotransmitters. Our studies will yield important insights into how these transporters operate, and how modulation of VGLUTs affects synaptic encoding and brain function. Because of observed profound regulation of VGLUTs in schizophrenia, depression and Parkinson’s disease, these findings will also contribute to diagnosis and treatment of mental illness.

Lay Summary