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Physiology and pathology of Glutamate-mediated neurotransmission in the brain

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The work in our laboratory focuses on one of the most prevalent means of communication between brain cells which is that mediated by Glutamate (Glu). This excitatory neurotransmitter exerts radically opposed properties: On the one hand, its smooth and physiological functioning allows to normally move, feel, perceive, learn and memorize, while on the other, its perturbed and pathological action may lead to cognitive, affective or motor deficits.

Our research has two major themes: one centers on the neuropathological effects of Glu with the aim to contribute in a practical way to the rational development of novel means to achieve a control of Glu actions in neurological disorders, the other focuses on the properties of Glu receptor channels in the production of short and long term modifications of neuronal function.

Boosting brain autoprotective mechanisms in neurodegenerative diseases

Brain functions depend entirely on the steady supply of blood-borne metabolites reaching every single cell in the brain via the extremely dense network on blood capillaries. Crossing the capillary endothelial cells that form the blood-brain barrier, the metabolites diffuse and are taken up by neuronal and glial cells to enable their various activities. However, brain metabolic and synaptic activities are also accompanied by the formation of potentially neurotoxic products that ought to be eliminated in order to allow the safeguarding and continuation of normal brain functions. The autoprotective mechanisms preventing the brain self poisoning are still poorly studied although it is recognized that the brain-blood barrier plays an important role.

Our laboratory is focusing on the study of the brain defense mechanisms against the excitatory neurotransmitter Glu that has been recognized to exert its neurotoxic properties in a wide range of neurodegenerative diseases such as stroke, head trauma, glaucoma and amyotrophic lateral sclerosis. For Glu, the defense mechanisms are based on sets of Glu transporters present not only on neurons and glia but also on the antiluminal side of the blood capillary endothelial cells.

We have shown that the Glu transporters present on the blood capillaries exert an autodefense mechanism since the injection in brain of radioactive Glu either in the lateral ventricles or by ventriculo-cisternal perfusion cause a rapid appearance of radioactivity in blood. This brain-to-blood Glu transport is the basis of several of our studies which include whole animal investigations, and the use of in vitro model and in silico model of the blood brain barrier. The existence of such a brain to blood Glu efflux now raises the possibility that boosting this transport activity could provide a novel approach to the treatment of those neurodegenerative diseases, such as stroke and head trauma, that are characterized by elevated and neurotoxic levels of Glu in brain. One way of boosting this transport activity is to administer either intracerebrally or preferably intravenously an enzyme that uses Glu as a substrate and by removing it from brain confers neuroprotection. Glu decarboxylase is one such candidate enzyme but since its enzymatic activity is impaired in the cerebrospinal fluid or blood environment, it is not effective enough. Therefore, we are submitting its encoding cDNA to 'in vitro evolution' and selection in order to obtain a Glu scavenging enzyme with therapeutic activities.

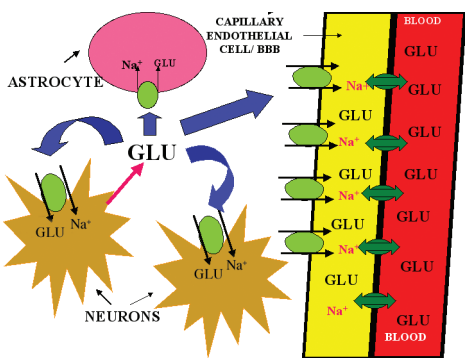

Fig. 1 *Schematic representation of the removal of Glu in brain. Glu transporters present on neurons and glia (astrocytes) as well as on the antiluminal side (brain side) of the capillary endothelial cells participate in the removal of Glu. These transporters co-transport Glu and sodium ions taking profit of the favorable sodium ion gradient. Altogether, Glu is effectively removed from brain into blood via the blood capillary endothelial cells in spite of an extremely unfavorable Glu gradient.*

Interaction of the NMDA-R cytoplasmic domain with subsynaptic proteins

It is well established that dendritic spines that carry Glu receptors undergo morphological changes upon exposure to Glu. This observation suggests that the activation of the dendritic Glu receptors by Glu is transduced within the dendritic spine to a contractile element within the cytoskeleton. Investigating the possible protein partners of the NMDA receptor subtype of Glu receptors, we have found that the actin-binding protein, spectrin, binds selectively to the C-terminal cytoplasmic domains of the NMDA-R subunits. These interactions are reversible and highly regulated mainly by phosphorylation reactions. The interaction with spectrin however is only one of the many possible interactions of the NMDA-R cytoplasmic domain since up to now more than 20 proteins have been shown to interact as well. Since one can rule out the simultaneous binding of all these proteins to the NMDA-R, we are studying the functional significance of these interactions to determine whether each of them provide the elements of a code allowing the individualization of synapses.

Selected Publications

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