

Jeudi 16 octobre à 11h30

Séminaire dans le cadre des candidatures “avenir blanc” du GIN.

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New insights into molecular and cellular mechanisms of epilepsy

Epilepsy is a common neurological disorder that is characterized by recurrent unprovoked seizures. There are many different types of epilepsy that can be divided by presumptive cause. Inherited idiopathic epilepsies arise from mutations in different genes. The majority of those genes code for voltage-dependent and ligand-gated ion channels.

For example, mutations in the genes encoding the potassium channels *KCNQ2* and *KCNQ3* have been identified in several families with benign neonatal familial convulsions, an autosomal dominant epilepsy of infancy. These K⁺-channels contribute to the native muscarinic-sensitive K⁺-current that regulates excitability of numerous types of neurons and KCNQ channel activators such as retigabine are effective in epilepsy treatment. Based on structural models, biochemical experiments and electrophysiological measurements, we have characterised in recent years the binding site and the mode of action of retigabine on KCNQ channels. Interestingly, *KCNQ2* and *KCNQ3* form homomeric and heteromeric channels. In different recent studies we identified a domain, which specifically regulates the subunit-specific assembly of these channels. This domain comprises two coiled-coil domains, assembles into tetramers and probably directs the tetramerization of functional channel complexes.

In a similar context our group has recently shown that mutations in a lysosomal membrane protein (LIMP-2) are associated with a syndrome that is characterized by a focal glomerulosclerosis and progressive myoclonic epilepsy associated with accumulation of storage material in the brain. We could also show that LIMP2 and specifically a coil-coiled region within its luminal domain serves as a receptor for transporting glucocerebrosidase to the lysosome, an enzyme that specifically degrades glucocerebroside. Dysfunction of the enzyme leads to accumulation of the substrate in Gaucher disease, which is the most common inherited lysosomal storage disease and can be also associated with neurological dysfunction, such as seizures.

Schenzer A, Friedrich T, Pusch M, Saftig P, Jentsch TJ, Grotzinger J, Schwake M (2005) Molecular determinants of KCNQ (Kv7) K⁺ channel sensitivity to the anticonvulsant retigabine. *J Neurosci* 25:5051-5060.

Schwake M, Jentsch TJ, Friedrich T (2003) A carboxy-terminal domain determines the subunit specificity of KCNQ K(+) channel assembly. *EMBO Rep* 4:76-81.

Schwake M, Athanasiadu D, Beimgraben C, Blanz J, Beck C, Jentsch TJ, Saftig P, Friedrich T (2006) Structural determinants of M-type KCNQ (Kv7) K⁺ channel assembly. *J Neurosci* 26:3757-3766.

Wehling C, Beimgraben C, Gelhaus C, Friedrich T, Saftig P, Grotzinger J, Schwake M (2007) Self-assembly of the isolated KCNQ2 subunit interaction domain. *FEBS Lett* 581:1594-1598.

Reczek D*, Schwake M*, Schroder J*, Hughes H, Blanz J, Jin X, Brondyk W, Van Patten S, Edmunds T, Saftig P (2007) LIMP-2 is a receptor for lysosomal mannose-6-phosphate-independent targeting of beta-glucocerebrosidase. *Cell* 131:770-783.

Lieu: Salle de conférences, Grenoble Institut des Neurosciences (GIN)

Bât. Edmond J. Safra, Chemin Fortune Ferrini CHU, La Tronche. Arrêt de tram : Hôpital A. Michallon, à côté des urgences et on accède au Bâtiment E.J. Safra en longeant les urgences et l'entrée Chartreuse de l'Hôpital.

Stationnement possible sur le parking du restaurant universitaire Le Chantourne

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Programme des séminaires : <http://neurosciences.ujf-grenoble.fr>