

# Synaptic dysfunction in migraine: novel approaches for drug development

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Migraine is a severe paroxysmal neurovascular disorder, affecting up to 16% of the Western population. Current migraine drugs are largely targeted towards the pain associated with the migraine headache, and their efficacy is limited. Furthermore, no biomarkers or direct gene involvement for migraine have been identified, despite a strong genetic component. Familial hemiplegic migraine (FHM) is a severe autosomal dominant subtype of migraine and an established genetic model to investigate the pathophysiology of the more common forms of migraine. The subtype if FHM1 is caused by mutations in the gene encoding neuronal voltage-gated Ca<sub>v</sub>2.1 (P/Q-type) calcium channels.

Co-morbidity of migraine with other neurological symptoms is high, and some FHM mutations are associated with ataxia, epilepsy or brain atrophy. Recently generated knock-in mice carrying the FHM1 S218L mutation are severely ataxic, whereas the FHM1 R192Q mutation does not yield any overt neurological phenotype, in accordance with the clinical manifestations of these mutations in humans.

Aberrant expression levels of both voltage-activated calcium channels and gamma-aminobutyric acid type-A (GABA-A) receptors have been suggested to underlie the ataxic phenotype of other Ca<sub>v</sub>2.1 calcium channel mutant mice, including *Tottering* and *Rolling Nagoya*.

We hypothesized that similar changes in expression levels of calcium channel and/or GABA-A receptor subunits are present in the cerebellum of S218L KI mice and that these may lead to abnormal cell homeostasis and excitability, and contribute to the onset of ataxia. Here we present a quantitative polymerase chain reaction (qPCR) study of the expression of both high- and low-voltage activated calcium channels, auxiliary subunits of voltage-gated Ca<sup>2+</sup> channels and GABA-A receptors in the cerebellum of R192Q and S218L KI mice. Furthermore, we analyzed the cerebellar GABA-A receptor complement using [<sup>3</sup>H] radioligand binding experiments, autoradiography and quantitative immunoblotting.

In ataxic FHM1 S218L KI we identified significant changes in calcium channel expression and the GABA-A receptor complement that were present at both the transcriptional and translational level. In contrast, non-ataxic FHM1 R192Q KI had normal cerebellar expression levels of all Ca<sup>2+</sup> channel and GABA-A receptor subunits. Our data support the hypothesis that the FHM1 S218L mutation causes chronic underlying synaptic dysfunction that results in an aberrant GABA-A receptor subunit complement in the cerebellum, thereby contributing to the ataxic phenotype.

Identification of novel pathways leading to synaptic dysfunction in migraine is a first step towards the development of novel, urgently needed prophylactic treatments for this devastating disease.

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