Unravelling the pathophysiology of calcium channel mutations causing neurological disorders

Voltage-gated calcium channels are molecules that play a key role in cell-to-cell communication and muscle contraction. They are divided into low voltage-activated (LVA or T-type) and high voltage-activated (HVA) channels, which may further be dissected into L, N, P/Q and R channels based on their sensitivity to drugs and toxins. Calcium channels constitute a heteromeric complex composed of a large pore-forming \( \alpha_1 \) subunit and four auxiliary subunits, \( \alpha_2/\delta \), \( \beta \) and \( \gamma \). Genes encoding the different subunits of the calcium channels have now been identified. For instance, the \( \alpha_1A \) subunit of the neuronal calcium channel is encoded by the \( CACNL1A4 \) gene; it contains four internal repeats (DI to DIV), each of them composed of six transmembrane segments (S1 to S6). Recently, P/Q type channels were shown to be splice variants of the \( CACNL1A4 \) gene (Bourinet et al., 1999). These channels are involved in the release of neurotransmitters from nerve terminals by allowing an influx of calcium which stimulates the exocytosis of synaptic vesicles (Augustine et al., 1998).

In recent years, mutations in the genes encoding \( \alpha_1 \) subunits of the voltage-gated calcium channels have been implicated in several human disorders. Familial hemiplegic migraine (FHM), episodic ataxia type 2 (EA-2) and spinocerebellar ataxia type 6 (SCA-6) are neurological disorders caused by mutations in \( CACNL1A4 \), whereas hypokalemic periodic paralytic and malignant hyperthermia are due to mutations in \( CACNL1A3 \), which encodes the \( \alpha_1 \) subunit of the skeletal muscle (Fontaine et al., 1997; Ptacek, 1998; Lehmann-Horn and Jurkat-Rott, 1999). Mutations in the mouse gene \( cacnl1a4 \), encoding the \( \alpha_1A \) subunit of the neuronal calcium channel, are also responsible for the tottering (tg) and leaner (tgla) phenotypes (Fletcher et al., 1996; Doyle et al., 1997). Homozygous tg and tgla mice exhibit severe ataxia and epileptic seizures. Alteration in the whole-cell calcium current has been found in Purkinje cells from tgla mutant mice (Dove et al., 1998; Lorenzon et al., 1998).

The tg mouse carries a missense mutation in the S4–S5 extracellular loop of domain II of the \( \alpha_1A \) subunit of the calcium channel. In general, missense mutations induce either a loss of physiological function, a gain of function in which the mutated protein acquires new properties, or a dominant-negative effect in which the protein inactivates the normal one.

In this issue of *Brain*, Plomp and colleagues report the consequences of the tg mutation on the transmitter secretion from motor nerve terminals, by analysing spontaneous and evoked release of acetylcholine at the neuromuscular junction (Plomp et al., 2000). They show that high-rate stimulation leads to an increased run-down of evoked acetylcholine release in homozygous tg mouse compared with the wild type. Interestingly, there is no change in evoked release at low rates of stimulation in homozygous tg mouse, clearly arguing in favor of a loss of function. The second observation of Plomp and colleagues is an increase of spontaneous acetylcholine release by approximately 100 and 40% in homozygous and heterozygous tg mice, respectively, which, in contrast, represents a gain of function. Altogether, when analysed at the synaptic level, the tg mutation seems to act simultaneously through both mechanisms of loss and gain of function. Nevertheless, the absence of motor deficiency in homozygous tg mice with altered acetylcholine release support the idea of compensatory mechanisms that may influence the clinical phenotype. Such mechanisms may vary between different tissues (and species) in which the mutated channel is expressed, thereby explaining the elaborate link between channel dysfunction and clinical phenotype.

Another important outcome of the study of Plomp and colleagues is that subclinical abnormalities might exist in other systems than those directly inferred from the clinical symptoms. If this is confirmed in human neurological disorders caused by \( CACNL1A4 \) mutations (FHM, EA-2 and SCA-6), precautions should be taken when using pharmacological agents which interfere with the neuromuscular function in these patients.

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References
Editorial


