A recurrent KCNQ2 pore mutation causing early onset epileptic encephalopathy has a moderate effect on M current but alters subcellular localization of Kv7 channels

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Résumé en anglais	Mutations in the KCNQ2 gene encoding the voltage-dependent potassium M channel Kv7.2 subunit cause either benign epilepsy or early onset epileptic encephalopathy (EOEE). It has been proposed that the disease severity rests on the inhibitory impact of mutations on M current density. Here, we have analyzed the phenotype of 7 patients carrying the p.A294V mutation located on the S6 segment of the Kv7.2 pore domain (Kv7.2(A294V)). We investigated the functional and subcellular consequences of this mutation and compared it to another mutation (Kv7.2(A294G)) associated with a benign epilepsy and affecting the same residue. We report that all the patients carrying the p.A294V mutation presented the clinical and EEG characteristics of EOEE. In CHO cells, the total expression of Kv7.2(A294V) alone, assessed by western blotting, was only 20% compared to wild-type. No measurable current was recorded in CHO cells expressing Kv7.2(A294V) channel alone. Although the total Kv7.2(A294V) expression was rescued to wild-type levels in cells co-expressing the Kv7.3 subunit, the global current density was still reduced by 83% compared to wild-type heteromeric channel. In a configuration mimicking the patients' heterozygous genotype i.e., Kv7.2(A294V)/Kv7.2/Kv7.3, the global current density was reduced by 30%. In contrast to Kv7.2(A294V), the current density of homomeric Kv7.2(A294G) was not significantly changed compared to wild-type Kv7.2. However, the current density of Kv7.2(A294G)/Kv7.2/Kv7.3 and Kv7.2(A294G)/Kv7.3 channels were reduced by 30% and 50% respectively, compared to wild-type Kv7.2/Kv7.3. In neurons, the p.A294V mutation induced a mislocalization of heteromeric mutant channels to the somato-dendritic compartment, while the p.A294G mutation did not affect the localization of the heteromeric channels to the axon initial segment. We conclude that this position is a hotspot of mutation that can give rise to a severe or a benign epilepsy. The p.A294V mutation does not exert a dominant-negative effect on wild-type subunits but alters the preferential axonal targeting of heteromeric Kv7 channels. Our data suggest that the disease severity is not necessarily a consequence of a strong inhibition of M current and that additional mechanisms such as abnormal subcellular distribution of Kv7 channels could be determinant.
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