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From frog oocytes to mammalian cells: substantial differences in modulation of Na_v1.4 channel slow kinetic behaviour by the β 1 subunit

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Background

Voltage gated sodium channels consist of an α subunit and several modulating β subunits. Upon depolarization, the α subunit first opens and then enters into different types of inactivated states. When expressed in mammalian cells, the β 1 subunit has been shown to modulate the kinetics of fast inactivation. Here, we tested whether a very stable inactivated state, which we refer to as ultra-slow inactivation (I_{us}), is subject to modulation by the β 1 subunit of the sodium channel. Previously, we showed that Na_v1.4 channels, containing the mutation K1237E in the selectivity filter, had enhanced entry into I_{us} when expressed in *Xenopus* oocytes. Coexpression of the β 1 subunit in this system had no effect on I_{us}. However, the kinetic behaviour of Na_v1.4 may vary between the *Xenopus* oocyte system and mammalian expression systems. As both systems are widely used in ion channel research, it appeared of interest to evaluate the kinetic effect of coexpression of β 1 in a mammalian expression system. Therefore, we tested whether I_{us} could be reproduced in TSA201 mammalian cells and whether it is subject to modulation by the β 1 subunit in this system.

Results

The time course of recovery from I_{us} was assessed by depolarizing the cells to -30 mV for 600 seconds, followed by repetitive 25 ms test pulses from -120 mV to -20 mV, at 5 s intervals. Fitting of a double-exponential function to the time course of recovery at -120 mV revealed that 45% of K1237E channels recovered with a time constant of ~140 s, characteristic for recovery from I_{us}. Coexpression of the construct with β 1 substantially reduced the fraction of channels recovering from I_{us} to 28%.

Conclusions

These results suggest that I_{us} can be reproduced in mammalian cells. However, unlike in *Xenopus laevis* oocytes, in a mammalian expression system this kinetic state can be modulated by the β 1 subunit.

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