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Meeting abstract

From frog oocytes to mammalian cells: substantial differences in modulation of $Na_V1.4$ channel slow kinetic behaviour by the β1 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 β1 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 (Ius), is subject to modulation by the β1 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 Ius when expressed in *Xenopus* oocytes. Coexpression of the β1 subunit in this system had no effect on Ius. 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 β1 in a mammalian expression system. Therefore, we tested whether Ius could be reproduced in TSA201 mammalian cells and whether it is subject to modulation by the β1 subunit in this system.

Results

The time course of recovery from Ius 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 Ius. Coexpression of the construct with β1 substantially reduced the fraction of channels recovering from Ius to 28%.

Conclusion

These results suggest that Ius 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 β1 subunit.

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