

Research report

Inhibitory action of thimerosal, a sulfhydryl oxidant, on sodium channels in rat sensory neurons

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Abstract

The effects of thimerosal, a sulfhydryl oxidizing agent, on tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) sodium channels in rat dorsal root ganglion neurons were studied using the whole-cell patch clamp technique. Thimerosal blocked the two types of sodium channels in a dose-dependent manner. The inhibitory effect of thimerosal was much more pronounced in TTX-R sodium channels than TTX-S sodium channels. The effect of thimerosal was irreversible upon wash-out with thimerosal-free external solution. However, dithiothreitol, a reducing agent, partially reversed it. Thimerosal shifted the steady-state inactivation curves for both types of sodium channels in the hyperpolarizing direction. The voltage dependence of activation of both types of sodium channels was shifted in the depolarizing direction by thimerosal. The inactivation rate in both types of sodium channels increased after thimerosal treatment. All these effects of thimerosal would add up to cause a depression of sodium channel function leading to a diminished neuronal excitability.

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Themes: Excitable membranes and synaptic transmission**Topics:** Sodium channels**Keywords:** Sulfhydryl oxidation; Thimerosal; Tetrodotoxin-sensitive; Tetrodotoxin-resistant; Sodium channel; Dorsal root ganglion**1. Introduction**

Voltage-gated sodium channel plays an important role in generation and conduction of action potential in excitable cells. Sodium channels on the axon initial segment of neurons determine the threshold for the action potential and affect the duration and frequency of repetitive firings. Also the release of neurotransmitters from presynaptic nerve terminal is influenced by sodium channel activity. The function of sodium channels is subject to modulation by various toxins, therapeutic drugs and neuromodulators.

Tetrodotoxin (TTX) is a potent neurotoxin that blocks voltage-gated sodium channels. Most sodium channels are blocked by TTX at the concentration range of 1–10 nM. However, sodium channels that are not sensitive to TTX exist in various tissues and in different animal species [32]. Rat dorsal root ganglion (DRG) neurons are endowed with

TTX-sensitive (TTX-S) as well as TTX-resistant (TTX-R) sodium channels [9,15,17]. Compared to TTX-S sodium current TTX-R sodium current exhibits slower time course of activation and inactivation, activates at higher voltage, and has a smaller single channel conductance. Pharmacologically TTX-R sodium channels are more sensitive to divalent cations (Co^{2+} , Mn^{2+} , Ni^{2+} , Cd^{2+} , Zn^{2+}) and pyrethroid insecticide but less sensitive to lidocaine than TTX-S sodium channels [20,21,25,28]. The TTX-R sodium channel in DRG neurons was cloned and its amino acid sequence revealed some homology with a cardiac sodium channel. According to in situ hybridization this channel was localized to DRG cells with smaller diameters [2,22,23].

Protein cysteine residues are reactive to the cellular redox state and participate in the regulation of cellular functions. The redox modification of cysteine sulfhydryl groups has been shown to alter the function of various ion channels. The activity of voltage-dependent potassium channels was increased by oxidation but decreased by

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