

Slobodan M. Todorovic, MD, PhD

Professor of Anesthesiology and Neuroscience,

University of Virginia, Charlottesville, VA 22901

Mail Box 800710

[st9d@virginia.edu](mailto:st9d@virginia.edu)

My research interests involve studies of pharmacology and function of voltage-gated calcium channels and particularly T-type (low-voltage-activated, LVA) channels in peripheral and central sensory transmission. Proposed roles for neuronal T-channels include promotion of calcium-dependent burst firing, generation of low-amplitude intrinsic neuronal oscillations, and elevation of calcium entry and boosting of dendritic signals. These channels are thought to contribute to neuronal pacemaker activity, wakefulness, and pain signaling and seizure susceptibility. Despite the fact that these channels were first described in peripheral sensory neurons and the thalamus, their function in sensory processing remains inadequately studied.

My research involves biophysical techniques to measure membrane currents (voltage clamp and current clamp recordings) from acutely dissociated rat sensory neurons and intact brain and spinal cord slices. We have cell lines available that express recombinant ion channel proteins which allow studies of the relationship between structure and function. At the system level, we directly examine the effects of Ca<sup>2+</sup> channel modulators on pain sensation following injection into peripheral receptive fields of sensory neurons in intact rats and rats with mechanically (chronic constrictive injury)- or metabolically (diabetic)-induced peripheral neuropathy, as well as knockout mice lacking T-type channels. Our future studies will investigate how modulation of T-type Ca<sup>2+</sup> channels in sensory and CNS neurons affects their function and how different anesthetic, analgesic and anticonvulsant agents selectively target particular classes of voltage-gated Ca<sup>2+</sup> channels. In particular, we are interested in testing new selective T-type channel blockers in vitro recordings from DRG, spinal dorsal horn and thalamic cells, as well as functional studies of nociception and anesthetic end points in vivo.

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Representative publications:

- 1) Nelson M.T., Joksovic P.M., Perez-Reyes E. and Todorovic S.M. The endogenous redox agent L-cysteine induces T-type  $\text{Ca}^{2+}$  channel-dependent sensitization of a novel subpopulation of rat peripheral nociceptors. *The Journal of Neuroscience*, 2005, 25(38):8766-75.
- 2) Jagodic MM, Pathirathna S, Nelson MT, Mancuso S, Joksovic PM, Rosenberg ER, Bayliss DA, Jevtovic-Todorovic V and Todorovic SM. Cell-specific alterations of T-type calcium current in painful diabetic neuropathy enhance excitability of sensory neurons. *The Journal of Neuroscience* 2007, 27(12):3305-3316.
- 3) Nelson MT, Woo J, Kang H-W, Barrett PQ, Vitko J, Perez-Reyes E, Lee J-H, Shin H-S, and Todorovic SM. Reducing agents sensitize C-type nociceptors by relieving high-affinity zinc inhibition of T-type calcium channels. *The Journal of Neuroscience* 2007, 27(31):8250–8260
- 4) Joksovic PM, Weiergraber M, Lee WY, Struck H, Schneider T and Todorovic SM. Isoflurane-sensitive presynaptic R-type calcium channels contribute to inhibitory synaptic transmission in the rat thalamus. *The Journal of Neuroscience* 2009, 29(5):1434-1445.