The Role of Slow and Persistent TTX-resistant Sodium Currents in Acute Tumor Necrosis Factor ? - Mediated Increase in Nociceptors Excitability.

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Created 12/25/2014
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Abstract:

Tetrodotoxin (TTX)-resistant sodium channels are key players in determining the input-output properties of peripheral nociceptive neurons. Changes in gating kinetics or in expression of these channels by proinflammatory mediators are likely to cause the hyperexcitability of nociceptivors and pain hypersensitivity observed during inflammation. Proinflammatory mediator, tumor necrosis factor ? (TNF?), is secreted during inflammation and is associated with the early onset, as well as long lasting, inflammation-mediated increase in excitability of peripheral nociceptive neurons. Here we studied the underlying mechanisms of the rapid component of TNF?-mediated nociceptive hyperexcitability and acute pain hypersensitivity in adult rats. Furthermore, TNF? rapidly and substantially increases nociceptive excitability in-vitro, by decreasing action potential threshold, increasing neuronal gain and decreasing accommodation. We extended on previous studies entailing p38 MAPK-dependent, increase in TTX-resistant sodium currents by showing that TNF? via p38 MAPK, leads to increased availability of TTX-r sodium channels by partial relief of voltage dependence of their slow inactivation, thereby contributing to increase in neuronal gain. Moreover, we showed that TNF? also in a p38 MAPK-dependent manner, increases persistent TTX-r current by shifting the voltage dependence of activation to a hyperpolarized direction, thus producing an increase in inward current at functionally critical subthreshold voltages. Our results suggest that rapid modulation of the gating of TTX-r sodium channels plays a major role in TNF?’s-mediated nociceptive hyperexcitability during acute inflammation and may lead to development of effective treatments for inflammatory pain, without modulating the inflammation-induced healing processes.

Journal:
Journal of Neurophysiology

Pagination:
jn.00652.2014

Date Published:
2014 Oct 29
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