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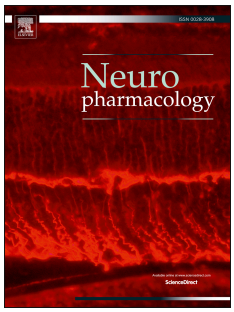

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A SNAP-25 cleaving chimera of botulinum neurotoxin /A and /E prevents TNFα–induced elevation of the activities of native TRP channels on early postnatal rat dorsal root ganglion neurons

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Keywords

Botulinum neurotoxin; TNFα; TRPV1; TRPA1; SNAP-25

ABSTRACT

Transient receptor potential (TRP) vallinoid 1 (TRPV1) and ankyrin 1 (TRPA1) are two transducing channels expressed on peripheral sensory nerves involved in pain sensation. Upregulation of their expression, stimulated by inflammatory cytokines and growth factors in animal pain models, correlate with the induction of nociceptive hyper-sensitivity. Herein, we firstly demonstrate by immuno-cytochemical labelling that TNFα augments the surface content of these channels on rat cultured dorsal root ganglion (DRG) neurons which, in turn, enhances the electrophysiological and functional responses of the latter to their specific agonists. A molecular basis underlying this TNFα-dependent enhancement was unveiled by pre-treating DRGs with a recently-published chimeric protein, consisting of the protease light chain (LC) of botulinum neurotoxin (BoNT) serotype E fused to full-length BoNT/A (LC/E-BoNT/A). This cleaves synaptosomal-associated protein of Mr 25k (SNAP-25) and reported previously to exhibit anti-nociceptive activity in a rat model of neuropathic pain. Low pM concentrations of this chimera were found to prevent the TNFα-stimulated delivery of TRPV1/A1 to the neuronal plasmalemma and, accordingly, decreased their incremental functional activities relative to those of control cells, an effect accompanied by SNAP-25 cleavage. Advantageously, LC/E-BoNT/A did not reduce the basal surface contents of the two channels or their pharmacological