The spinal effects of the VGF-derived peptide TLQP-21 are mediated by the Complement 3a receptor

20a

Suzanne Doolen, PhD[1] • Jennifer Cook[2] • Maureen Reidlc[3] • Kelley Kitto[3] • Shinichi Kohsaka[4] • Christopher Honda, PhD[3] • Carolyn Fairbanks, PhD[5] • Bradley Taylora , PhD[6] • Lucy Vulchanova, PhD[3]

[1]PGY, University of Kentucky • [2]Graduate Program in Neuroscience, University of Minnesota • [3]Neuroscience, University of Minnesota • 4Neuroscience, National Institute of Neuroscience, Tokyo, Japan [5]Neuroscience, Pharmaceutics, and Pharmacology, University of Minnesota • [6]Physiology, University of Kentucky

VGF (non-acronymic), a granin-related neurosecretory protein, and its bioactive proteolytic peptide fragments, such as TLQP-21, contribute to neuroplasticity in depression, learning and memory, energy balance, and chronic pain. The present study determines for the first time that complement 3a receptor (C3aR1), expressed on dorsal horn microglia, is a signaling receptor for the analgesic actions of VGF peptides. We show that administration of TLQP-21 to the mouse by the intrathecal route, or to the mouse spinal cord slice by superfusion, produces pronociceptive effects and Ca2+ mobilization, respectively. Both of these actions were blocked with the C3aR1 inhibitor, SB290157. TLQP-21-induced Ca2+ mobilization was localized to microglia with the use of, double-label immunohistochemistry, calcium imaging in slices from mice expressing eGFP under the control of the Iba1 promoter, and with studies in primary microglial cultures. TLQP-21/C3aR1 calcium signaling and spinal C3aR1 expression were increased following peripheral nerve injury, suggesting a relationship to neuropathic pain. We propose a novel neuro-immune signaling pathway , involving TLQP-21-induced activation of microglial C3aR1 that contributes to spinal neuroplasticity following peripheral nerve injury.