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Intrathecal Administration of an Anti-nociceptive Non-CpG Oligodeoxynucleotide Reduces Glial Activation and Central Sensitization

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Abstract

Inflammatory pain associates with spinal glial activation and central sensitization. Systemic administration of IMT504, a non-CpG oligodeoxynucleotide originally designed as an immunomodulator, exerts remarkable anti-allodynic effects in rats with complete Freund´s adjuvant (CFA)-induced hindpaw inflammation. However, the anti-nociceptive mechanisms of IMT504 remain unknown. Here we evaluated whether IMT504 blocks inflammatory pain-like behavior by modulation

of spinal glia and central sensitization. The study was performed in Sprague Dawley rats with intraplantar CFA, and a single lumbosacral intrathecal (i.t.) administration of IMT504 or vehicle was chosen to address if changes in glial activation and spinal sensitization relate to the pain-like behavior reducing effects of the ODN. Naïve rats were also included. Von Frey and Randall-Selitto tests, respectively, exposed significant reductions in allodynia and mechanical hypersensitivity, lasting at least 24 h after i.t. IMT504. Analysis of electromyographic responses to electrical stimulation of C fibers showed progressive reductions in wind-up responses. Accordingly, IMT504 significantly downregulated spinal glial activation, as shown by reductions in the protein expression of glial fibrillary acidic protein, CD11b/c, Toll-like receptor 4 (TLR4) and the phosphorylated p65 subunit of NFκB, evaluated by immunohistochemistry and western blot. In vitro experiments using early post-natal cortical glial cultures provided further support to in vivo data and demonstrated IMT504 internalization into microglia and astrocytes. Altogether, our study provides new evidence on the central mechanisms of anti-nociception by IMT504 upon intrathecal application, and further supports its value as a novel anti-inflammatory ODN with actions upon glial cells and the TLR4/NFκB pathway. Intrathecal administration of the non-CpG ODN IMT504 fully blocks CFA-induced mechanical allodynia and hypersensitivity, in association with reduced spinal sensitization. Administration of the ODN also results in downregulated gliosis and reduced TLR4-NF-κB pathway activation. IMT504 uptake into astrocytes and microglia support the concept of direct modulation of CFA-induced glial activation.

Keywords: Complete Freund's adjuvant; IMT504; Inflammatory; Intrathecal administration; NFκB; Spinal cord.

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