Thrombospondins as a Target to Treat Neuropathic Pain

Tech ID: 27260 / UC Case 2008-708-0

BRIEF DESCRIPTION

Neuropathic pain is a common problem, though, there are few existing pain medications that have specific targets to treat this type of pain, and often lack efficacy and tolerance. The invention identifies specific proteins and related genes as targets for treating neuropathic pain in an animal model.

FULL DESCRIPTION

Neuropathic pain resulting from injured peripheral nerves upregulates Thrombospondin (TSP) protein, especially the TSP-4 gene expression, in the spinal cord. The functional role and mechanism of upregulated TSP following nerve injury and chronic pain is unknown. Few existing neuropathic pain medications have specific targets and often lack efficacy and tolerance of (potentially dangerous) side effects.

The inventor has identified TSP antibodies, antisense oligonucleotides, and related molecules against TSP as novel targets for preventing and reversing chronic pain. In an animal model, one side of the spinal nerve is ligated (nerve-injured) while the other side is left non-injured (control). Molecular agents were administered intrathecally into control or nerve-injured rats. Pain thresholds were assessed by paw withdrawal to mechanical stimulation whereby animals experiencing pain would have reduced paw withdrawal thresholds.

Antisense oligonucleotides against TSP-4 gene sequences reversed chronic pain in nerve-injured rats while preserving sensitivity in the control side.

Control injection of mismatch oligonucleotides had no effect on preventing or reversing chronic pain. Additionally, TSP-1 proteins caused dose dependent neuropathic pain in control rats; heat-inactivated TSP-1 had no effect. TSP-4 antibodies reversed established chronic pain in a dose dependent manner if animals started treatment after onset of induced pain and prevented pain development if animals started treatment before injury; heat-inactivated TSP-4 antibodies had no effect.

The development of target specific and safe medications relies on greater understanding of neuropathic pain mechanisms. TSP expression induced by nerve injury appears to have implications in pain processing and blocking its functions or pathways can offer therapeutic value in treating neuropathic pain.

PATENT STATUS

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<td>United States Of America</td>
<td>Issued Patent</td>
<td>8,491,897</td>
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STATE OF DEVELOPMENT

§ Concept only, the function and mechanism of TSP induced by nerve-injury in chronic pain remains unknown

§ In vivo studies revealed:

- In control rats, TSP-1 proteins reduced pain in a dose dependent manner
- In nerve-injured rats, only active TSP-4 antibodies reversed pain unlike inactive TSP-4 antibodies
- Daily treatment of TSP-4 antibodies before injury delayed the onset of pain post injury
- Daily treatment of TSP-4 antisense oligonucleotides initiated before injury reversed pain while preserving sensitivity on the control side; control mismatch oligonucleotides had no effect

ADVANTAGES

- Treatment and intervention for neuropathic pain and nerve injury-related disorders
- Development of methods and molecules such as antibodies, small molecules, and antisense oligonucleotides targeting TSP as therapeutic agents

RELATED MATERIALS
Crosby ND; et. al. Thrombospondin-4 and Excitatory Synaptogenesis Promote Spinal Sensitization after Painful Mechanical Joint Injury. Exp Neurol. 2015, 264, 111. - 12/05/2014

