2013 Pain Day Poster Competition

Basic Science:

Inhibiting Inflammation With Ccr2/5 Antagonist Reverses Mechanical And Cold Allodynia In Painful Diabetic Neuropathy Rats

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Painful diabetic neuropathy (PDN) is a common complication of diabetes which adversely affects patients' daily life and represents a major public health problem. Although this painful signal is believed to originate in the peripheral nervous system, the precise cellular mechanisms of chronic pain associated with PDN remain poorly understood. Inspired by the critical contribution of inflammation in injury models of neuropathic pain, here we reasoned that if inflammation is also engaged in the pathogenesis of diabetic neuropathic pain, then 1) infiltration of immune cells in damaged nerves and/or activation of spinal microglia should coincide with the development of pain; 2) inhibiting inflammatory response in the peripheral and/or the central nervous system should reduce chronic pain. To test the hypothesis, we first used behavioral and molecular/cellular approaches to explore chronic pain development and inflammatory reaction in Streptozotocin (STZ) induced diabetic rats. Our results showed that following the induction of diabetes, rats exhibited persistent mechanical and cold allodynia (up to five months post-induction). The levels of inflammatory molecules, including cytokines, IL-1□, TNF-□; chemokines CCL2, CCL3; and chemokines receptors CCR2 and CCR5 were dramatically increased in sciatic nerves. Microglia in the spinal cord dorsal horns became activated with hypertrophic morphology and an increase in microglial cell number. CCL2 and CCL3 are two chemokines well known in mediating immune cell trafficking and immune response in the context of neuropathic pain. Oral administration of RAP-103, a CCR2/CCR5 dual antagonist for 7 days inhibited PDN associated inflammation by reducing significantly all examined inflammatory mediators. The effect of RAP-103 is more pronounced at peripheral nerves. In coincidence, the treatment with RAP-103 (0.5-0.02mg/kg b.w., daily, for 7 days) resulted in a complete reversal of established hypersensitivity in STZ rats. All these results suggest that inflammation has a mechanistic role in diabetic neuropathic pain. CCR2 and CCR5 may be promising future targets for treatment.