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C5A/C5AR1 SIGNALING DRIVES MICROGLIA-DEPENDENT HYPEREXCITABILITY IN SUPERFICIAL DORSAL HORN NEURONS AFTER SPARED NERVE INJURY

Background. The complement system is a part of innate immunity activated by inflammation via its complement fragment C5a. After nerve injury, C5a and C5aR1 are upregulated in dorsal horn (DH) microglia, amplifying neuroinflammation and pain hypersensitivity. Blocking C5aR1 reduces allodynia and hyperalgesia, proving this pathway is a promising therapeutic target in neuropathic pain. **Methods.** Lamina I neurons were studied in isolated adult mouse lumbosacral spinal cord (SC) using a whole intact preparation with preserved L5/L4 roots and positioned for lamina I access for electrophysiological recordings. **Results.** Using a mouse spared nerve injury (SNI) model, we examined how C5a/C5aR1 signaling contributes to spinal sensitization. Single intrathecal administration of the selective C5aR1 antagonist PMX205 produced a rapid analgesic effect, indicating that this pathway is required for maintenance of neuropathic pain. In intact SC preparations, multiphoton Ca^{2+} imaging showed that C5a evoked rapid transient Ca^{2+} elevations in microglia. Patch-clamp recordings further showed that C5a increased excitability of superficial DH neurons, by enhancing dorsal root-evoked and spontaneous firing, triggering burst activity in a subset of cells. These effects were associated with a reduced action potential (AP) threshold and prolonged firing responses, whereas excitatory synaptic input changed little, suggesting that C5a primarily alters intrinsic membrane properties rather than synaptic drive. Voltage-ramp analysis supported this by revealing shifts in inward current activation consistent with increased membrane excitability. Across more than two thousands of recorded AP from C5a, sham-, and PMX205-treated preparations, multiple AP parameters changed significantly, with particularly strong effects on peak amplitude, resting membrane potential, and spike threshold. These data identify C5a/C5aR1 signaling as a key modulator of microglia-neuron communication and DH hyperexcitability after nerve injury. **Conclusions.** C5a/C5aR1 signaling promotes neuropathic pain after SNI by activating microglia and increasing intrinsic excitability of superficial DH neurons. Pharmacological blockade of C5aR1 with PMX205 produced analgesia, supporting this pathway as a promising therapeutic target for neuropathic pain. **Grants/Fundings.** NIH 1R01NS113189–01, NASU0124U001557, NASU0125U001123.

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