UP-REGULATION OF HIGH MOBILITY GROUP BOX-1 IN SPINAL CORD FOLLOWING PERIPHERAL NERVE INJURY

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INTRODUCTION: Peripheral nerve injury induces neuropathic pain through the up-regulation of inflammatory mediators in the spinal cord and dorsal root ganglia. The novel inflammatory cytokine high mobility group box 1 (HMGB1) is released actively by activated macrophages/monocytes or passively by necrotic cells into the extracellular milieu; and is associated with the pathogenesis of many CNS diseases. Nonetheless, little is known about the biological effects of HMGB1 in the peripheral nerve injury. In an attempt to understand the potential role of HMGB1 in triggering spinal glia activation and its contribution to the development of neuropathic pain, we investigated the HMGB1 expression in the spinal cord using a rat model of the condition spared nerve injury (SNI).

METHODS: The protocol for this experiment was approved by our animal care and use committee. Under general anesthesia, 30 male Sprague-Dawley rats weighing 250-350 g were randomly divided into 5 groups to receive sham operation and 1, 4, 7 and 14 days after SNI. The development of mechanical hypersensitivity was measured by using von Frey hair filaments. HMGB1 and pERK expression in the spinal cord were assessed by western blotting or immunohistochemistry studies. Microglia activation was examined by OX-42 immunofluorencence staining. The results were analyzed by ANOVA with repeated measures followed by the Dunnett test. Differences were considered to be significant at $P < 0.05$.

RESULTS: A reduction in paw mechanical withdrawal threshold was observed and western blot analysis confirmed an increase in HMGB1 protein expression in the spinal cord after SNI. Immunohistochemistry for HMGB1 revealed that SNI-induced HMGB1 expression increased in the ipsilateral dorsal horns. Immunofluorencence staining for HMGB1 and neuron marker Neu-N indicates the most prominent increase was in the superficial laminas I-III neuron of the dorsal horn. Neuronal HMGB1 induction was associated with translocation from the nucleus to the cytoplasm, and was followed by surrounding microglia activation. The extracellular signal-regulated kinase (ERK) was significantly activated in ipsilateral dorsal horn after SNI surgery.

DISCUSSION: The present study demonstrated that HMGB1 was overexpression in the dorsal horn neurons and ventral horn motor neurons after spared nerve injury and might be related with microglia activation. Our results suggested that neuronal HMGB1 might serve a trigger for neuron-glia interaction, and provided evidence for a novel mechanism involved in neuropathic pain induced by nerve injury. Targeting HMGB1 signaling may be an important therapeutic strategy in peripheral nerve injury induced neuropathic pain.