Inhibition of NADPH oxidase attenuates functional deficits in middle-aged mice after spinal cord injury

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The average age at the time of spinal cord injury (SCI) has steadily increased from the average age of 29 years old in the 1970's to the current age of 42 years old. Recent findings from our group and others demonstrate that middle-aged mice exhibit worse functional deficits and exacerbated tissue damage after SCI. This is associated with age-dependent increases of reactive oxygen species (ROS) production, NADPH oxidase (NOX) activity and pro-inflammatory macrophage activation. Despite these age-specific differences, clinical therapies are being examined in individuals regardless of age and are based upon preclinical data generated almost exclusively using young animals. The purpose of the current study is to test the extent to which age affects the efficacy of SCI treatment. Specifically, we hypothesize that the effectiveness of apocynin, a NOX inhibitor for SCI, is age-specific. We applied mild-to-moderate contusion injury at the thoracic level (T9 laminectomy, 50 kdyn Infinite Horizons) to 4-month-old (4MO) and 14 MO mice. We treated mice with apocynin (5 mg/kg, intraperitoneal injection) or vehicle (1% DMSO) at 1 and 6 hours post injury, then daily for 1 week. We examined the effect of apocynin treatment on functional and anatomical recovery from SCI. Our results show that apocynin effectively improves functional recovery and decreases lesion volume in 14 MO but not in 4 MO SCI mice. This suggests that apocynin may exhibit age-dependent neuroprotection by blocking excessive NOX-mediated ROS production. To the best of our knowledge, our data is the first to identify age as a critical regulator for SCI treatment efficacy. Age therefore needs to be considered as an important clinical variable to tailor therapeutic interventions and best serve the diverse SCI community.