HINDPAW INCISION-RELATED HYPERALGESIA IN ADULTHOOD IS INCREASED BY PRIOR NEONATAL INCISION: SPINAL MICROGLIAL ACTIVATION AND MODULATION BY MINOCYLCLINE


incision
neonate
microglia

Tissue injury in a critical neonatal period can produce long-term alterations in sensory processing and enhance sensitivity following repeat injury in later life. Using the plantar hindpaw incision model in the rat pup, we evaluated the response to repeat incision in adulthood to determine if prior neonatal surgical injury alters the degree of postoperative hyperalgesia and is associated with changes in spinal microglial activation.

Methods: Plantar hindpaw incision was performed in anesthetised postnatal day (P)3 rats. Repeat (P3 + adult) incision, single incision in adult, and non-incised controls were compared. Hyperalgesia was quantified by behavioural thresholds and by recording flexion reflex EMG responses to hindpaw mechanical stimuli. Microglial activity in the dorsal horn was determined by Iba1 immunoreactivity following incision or tibial nerve C-fibre electrical stimulation in adults with and without prior neonatal incision. Effects of systemic and spinal administration of minocycline (100 mg/kg, i.p. or 0.35 mg/kg, i.t.) one hour prior to incision and one hour prior to EMG recordings) were compared across groups.

Results: Reflex sensitivity was significantly greater in the repeat versus single incision groups. Iba1 immunoreactivity in the dorsal horn was increased 3 days following adult single incision but was apparent earlier (24 hours) and was more marked at 3 days after repeat incision. Pre-treatment with intrathecal minocycline blocked hyperalgesia in the repeat incision group but had no effect 24 hours following single incision. Intraperitoneal minocycline reduced hyperalgesia in both the single and repeat incision group.

Conclusions: Neonatal hindpaw incision is associated with an enhanced response to subsequent injury that persists until adulthood. Alterations in the time course and degree
of microglial activation in the spinal cord are likely to contribute to the longterm enhancement of responses to repeat surgery. Effects of intrathecal minocycline in the repeat incision group suggest centrally-mediated inhibition of microglial activation, whereas systemic minocycline may have peripheral anti-inflammatory effects. These studies have implications for perioperative outcomes in children and adults with prior neonatal surgery.