

The Role of Cyclooxygenase-1 in Postoperative Mechanical Allodynia is Developmentally Regulated

H.M. Prout, BS; D.G. Ririe, MD; J.C. Eisenach, MD

Dept. of Anesthesiology, Wake Forest University School of Medicine, Winston-Salem, NC 27157-1009

Introduction: The paw incision in the rat has been established as a reproducible model to study acute postoperative pain (1). Age-dependent differences in behavioral responses using the paw incision model have been established (2). However, the etiology of the differences in these behavioral responses is unclear. Cyclooxygenase-1 (COX1) plays a potentially important role in the inflammatory response to peripheral nerve injury in mature rats (3,4). Furthermore, COX1 has been shown to be up-regulated in the spinal cord following the paw incision in the mature animal (5). However, the role of COX1 in the age-dependent behavioral responses to acute postoperative pain has not been studied. We hypothesize that developmental differences in response to inhibition of COX1 exist in this model of postoperative pain.

Methods: After approval from the Animal Care and Use Committee, male Sprague-Dawley rats at 2- and 4-weeks (wk) of age were anesthetized with 2% halothane. All animals underwent a left paw incision as described previously (2). After a 2-hr recovery period the rats received either: 1000, 300, or 100 $\mu\text{g}/\text{kg}$ of SC560 (COX1 selective inhibitor) in 87% DMSO/13% deionized water (vehicle) or vehicle control in a volume $1\mu\text{L}/\text{g}$ of body weight subcutaneously in the shoulder. Mechanical allodynia was assessed using calibrated von Frey filaments using a modification of the up-down method at baseline before surgery and 2-hr after surgery and then at 1, 2, and 4 hr. Data were analyzed using repeated measure ANOVA and presented as means with standard error of the mean thresholds in grams.

Results: The baseline thresholds before surgery were 5.9 ± 0.4 g in the 2-wk-old and 19 ± 0.8 g in the 4-wk-old animals. Withdrawal threshold to von Frey filament testing decreased significantly after surgery in animals of all ages. A dose-response curve (N=7 each dose) determined that the maximum analgesic effects of SC560 occurred at 1000 $\mu\text{g}/\text{kg}$ at 2 hr in the 4-wk-old animals (Figure 1). The vehicle control and the 1 mg/kg groups were compared at 2 hr for contrast in analgesic effects (N=7 each group). The 2- and 4-wk-old vehicle control groups had no significant change in pain threshold over the course of the experiment. COX1 inhibition produced an increase in threshold in the 4-wk-old animals compared to the control group ($p < 0.0024$), while it produced no effect in the 2-wk-old animals (Figure 2). The difference between the 2- and 4-wk-old responses was significant ($p < 0.0001$).

COX1 Inhibitor Dose-Response at 2 Hours

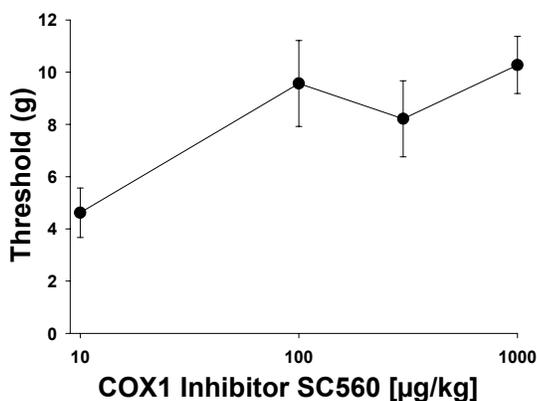


Figure 1. 4-week-old dose-response curve at 2 hours.

Threshold Response vs Time (SC560 1 mg/kg)

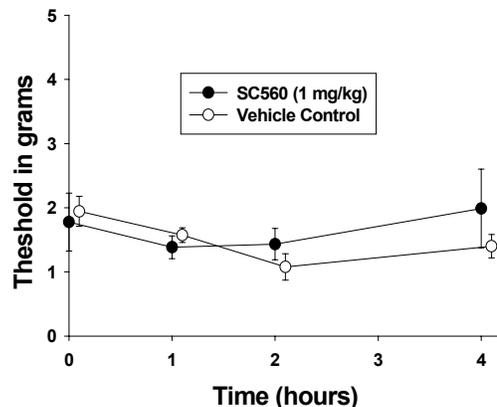


Figure 2. COX1 inhibition in 2-week-old rats at 2 hours. Vehicle and SC560 (1 mg/kg)

Discussion: In 4 wk-old rats, COX1 inhibition demonstrated a significant reduction in postoperative pain. The reduction in pain in the 4-wk-old group as measured by mechanical thresholds was significant with the maximum effect occurring at 2 hr. COX1 inhibition in the 2-wk-old group produced no significant reduction in pain. Whether lack of response to COX1 inhibition in the 2-wk-old animals is a result of age-specific developmental expression in the peripheral and/or central nervous system is unclear. Increased expression of COX1 in the spinal cord of the mature animals following paw incision suggests the effects of COX1 inhibition may be spinally mediated (5). Further studies to determine the location and expression of COX1 in animals at different stages of development will help understand postoperative pain and its treatment during development.

References: 1) Pain 1996;64(3):493-501; 2) Anesthesiology 2003;99:443-448; 3) Cell 1995;83:483-492; 4) Brain Res 2002;937:94-99; 5) Anesthesiology 2003;104:15-23.