

Neuroprotective effect of Sonic hedgehog signaling in glucocorticoid-induced neonatal cerebellar injury through an 11 β HSD-2 dependent mechanism

Vivi M. Heine¹ and David H. Rowitch^{1,2}

¹Institute for Regeneration Medicine, UCSF, 513 Parnassus Avenue, San Francisco CA 94143; ²Division of Neonatology, Departments of Pediatrics and Neurosurgery, UCSF, 533 Parnassus Avenue, San Francisco, CA 94143

Objectives - Glucocorticoids (GC) are administered to human fetuses at risk of premature delivery and infants with life-threatening respiratory and cardiac conditions. Despite ongoing concern about adverse effects of GC treatment on the developing human brain, the molecular mechanisms underlying GC-induced brain injury are unclear. The developing cerebellum is one of the regions in the brain that is sensitive to high GC levels. Sonic Hedgehog (Shh) pathway activation has been shown to regulate the complexity of cerebellar foliation, raising the possibility that increased levels of Shh-Smo signaling might counteract anti-proliferative effects of GC treatment.

Methods - To study the effects of GC treatment on early neonatal cerebellar development involving multiple courses, we treated C57BL6J mouse pups with Dexamethasone (Dex) for one week daily from P0 - P7. We used a dose of 0.1 mg/kg, within the range (0.1-0.5 mg/kg) used for human neonates in the United States. To increase levels of Shh-Smo signaling in cerebellar granule neuron precursors (CGNP), we generated transgenic mice in which constitutively activated Smo (*SmoM2^{fl/fl}*) is produced specifically in CGNP under the control of *Math1-cre*.

Results - We identify cross-antagonistic interactions of Shh and GC signaling in proliferating CGNP. GC treatment inhibits Shh-induced proliferation and down regulates N-myc and D-type cyclin protein expression in CGNP. Conversely, Shh signaling antagonizes glucocorticoid effects by induction of 11 β -Hydroxysteroid Reductase Type 2 (11 β HSD2), which inactivates corticosterone, hydrocortisone and Prednisolone but not the synthetic GCs Dexamethasone and β -methasone.

Conclusions - Our findings indicate that Hedgehog signaling is neuroprotective in the setting of GC-induced neonatal brain injury. They further lead to the proposal that 11 β HSD2-sensitive GCs (hydrocortisone/Prednisolone) should be used in preference to Dexamethasone in neonatal infants because of potentially reduced neurotoxicity.