Intervention after Neonatal Brain Injury: Experimental Evidence

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Immature Animal Models of Cerebral Palsy

• Pre- or postnatal hypoxia-ischemia (HI) models
• With functional outcome
  – Rabbits (global injury)
  – Rats and mice (unilateral injury)
• Without functional outcome
  – Fetal lambs
  – Piglets
Neonatal HI Models with Functional Outcome (1)

- Rabbit: in-utero transient (40 min) aortic occlusion (upstream of uterine arteries) on E22 (70% gestation; term=31.5 d) or E29 (79% gestation)
  - Tan, Derrick, et al. (Evanston-Northwestern)
  - White matter injury in corpus callosum, internal capsule, corona radiata
  - Neonatal spasticity or motor deficits in ~70% of survivors, variable severity; need intensive care
  - No long term outcome; no “cognitive” measures (yet)
Neonatal HI Models with Functional Outcome (2)

- Rat - postnatal day 7 unilateral carotid ligation + timed hypoxia exposure (Rice, Vannucci and many others)
  - P7 brain similar to third trimester human
  - Cortical, striatal and hippocampal damage
  - Contralateral sensorimotor deficits, not spastic, detectable in “infancy”
  - Cognitive deficits (spatial learning and memory) detectable in juvenile, adult
P7 Rat HI: MRI and Pathology

A; Diffusion weighted imaging, striatal level P8
B: T2-weighted imaging, P8
C: T2-weighted imaging, P22
D: Nissl stained section, adult
P7 Rat HI: Range of Pathology

Non-HI

Mild

Mod

Sev
Modeling Behavioral Intervention

• Early Neonatal Handling (Seymour Levine, Michael Meaney)
  – Increased maternal care-giving pre-weaning
  – Improved stress axis feedback regulation
  – Improved learning and memory in aging

• When applied after P7 rat hypoxia-ischemia, post-HI handling reverses post-HI learning deficits (Chou et al., 2001)
  – No effect on swim speed
Modeling Motor Intervention

• Why?
  – Understand mechanisms
  – Support more human trials

• Current modeling projects:
  – Constraint induced movement therapy
  – Treadmill training
Targeted Motor Intervention

• Constraint-induced movement therapy
  – (Early) forced use of impaired limb
• Commonly used in adult stroke victims with hemiplegia
• 3 randomized trials in hemiplegic CP (n=94)
  – 1 with significant effect
  – still “experimental” (Cochrane Database, 2007)
• Mechanism of effect unknown
• Can we model this in neonatal animals, to investigate mechanisms?
Targeted Motor Stimulation

• Unilateral (right) HI, P7 rats (1.5 h or 2 h)
• Repetitive stimulation of left vibrissae, twice daily, x 5 wks
• 2 Control groups: “Vestibular”; “testing only”
• 1º Outcome: Weekly testing: Forepaw placing response P14-63
• 2º Outcome: Adult testing: Rotarod (gait); Vertical Cylinder (forepaw preference); Watermaze (spatial learning)
Summary

• Forced use paradigm targeting affected forelimb accelerated recovery of reflex forepaw placing in that limb.
• Other effects: coordinated forepaw use in cylinder restored to normal
• Benefit not confounded by difference in baseline severity of injury, nor by difference in injury progression (MRI)