Steroids and Injury to the Developing Brain

Net Harm or Net Benefit?

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KEYWORDS

• Brain injury • Cerebral palsy • Controversy • Development • Glucocorticoids • Infant • Outcomes • Premature infant

KEY POINTS

- Steroid effects on the brain mimic an inverse-U–shaped curve, because deleterious effects result from both glucocorticoid insufficiency and/or excess glucocorticoid tissue exposure.
- The effects of glucocorticoids on the developing central nervous system are a function of both the stage of development and duration of exposure.
- The beneficial effects of glucocorticoids are optimal when given to sick premature infants in a critical window before 32 weeks' postmenstrual age.
- Glucocorticoids have net beneficial effects when given shortly after the first week of life to premature infants at high risk for severe chronic lung disease.
- The challenge is to identify infants at high risk for bronchopulmonary dysplasia (BPD) early in their course and to administer a dose that attenuates the progression of BPD.

INTRODUCTION

Glucocorticoids, commonly referred to as *steroids*, are widely used in neonatal-perinatal medicine. They are prescribed to pregnant women at risk for premature birth, and sometimes to infants with significant airway or lung disease, refractory hypotension, or septic shock. Preterm infants are at high risk for brain injury, morbidity, and mortality. Steroids are thought to attenuate some of these risks.[1,2] However, steroid regimens used vary widely, from a single short course of antenatal steroids given to the mother early in the third trimester, to repeated or prolonged courses of steroids

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given over weeks to the premature infant. As more data have accumulated regarding the long-term outcomes of infants exposed to steroids, concern has been increasing about neurodevelopmental impairment after exposure to steroids in certain settings. This article summarizes some of the experimental and clinical findings, and explores the complex nature of the relationship between steroids and brain injury, with a focus on the premature brain.

OVERVIEW OF BRAIN DEVELOPMENT

Normal brain development requires a well-orchestrated ontogeny of cellular proliferation, migration, differentiation, angiogenesis, synaptogenesis, myelination, and apoptosis.[3] Neurogenesis remains active well into adulthood in the subventricular zone and hippocampal dentate gyrus.[4] Neuronal progenitor cells migrate from their sites of origin and become mature integrated neurons. Early-stage neuronal progenitor cells maintain an active cell cycle and can either divide or die via apoptosis. As progenitor cells mature, they exit the cell cycle and commit to differentiate.[5] A large number of migrating neurons populate a transient subcortical layer known as the *subplate zone*. Other neurons enter the cortical plate and integrate into neuronal circuits. Synaptic connectivity is essential to maintain survival for cortical neurons. Most subplate neurons involute through apoptosis toward late gestation and in infancy. Oligodendrocyte progenitor cells follow neuronal tracts and mature to form myelin. Cerebral vascular endothelial cells, pericytes, and astrocytes promote angiogenesis to form neurovascular units that will support neurons and form the blood–brain barrier.[6,7] The ontogeny of the developing nervous system is under tight regulation by intrinsic, paracrine, endocrine, and external modulators. Perturbations in any of these factors could result in long-term consequences that affect the structure and function of the developing central nervous system (CNS).[3]

NEUROTROPHIC EFFECTS OF STEROIDS

Steroids are essential for maturation and survival of several cell types in the CNS. Adrenalectomy in adult rats results in massive cell death in the dentate gyrus and decreases the number of dendritic branch points.[8,9] Corticosterone replacement after adrenalectomy reverses these processes.[9] Corticosterone administration accelerates neuronal migration of cerebellar granule cells and enhances cerebellar Purkinje cell growth in the offspring. This treatment also accelerates the emergence of perinucleolar rosettes forming accessory nucleolar bodies of Cajal.[10] The emergence of this structure signifies increases in transcriptional activity present during the late stages of neuronal maturation.[11] Corticosterone application early in development also accelerates the differentiation of membrane electrical properties in embryonic chick neurons.[12] In addition, glucocorticoids activate brain-derived neurotrophic factor receptor (Trk) tyrosine kinases and induce the expression of thyroid hormone–dependent transcription factor Kruppel-like factor 9 gene.[13–15] These events are implicated in the plasticity of hippocampal neurons and postnatal development.[13–15] Short-term corticosterone exposure increases synaptogenesis in the developing cortex. Reducing endogenous glucocorticoid activity decreases spine process turnover, and corticosterone reverses this process.[16,17] Therefore, corticosterone seems to accelerate neuronal maturation. Glucocorticoids also induce oligodendrocyte precursor differentiation[18] and increase oligodendroglial marker expression during myelinogenesis.[19–21] In summary, steroids exert important trophic effects on cell survival, differentiation, maturation, and synaptogenesis (**Box 1**).