The Equine Neonatal Central Nervous System

Development and Diseases

Brett S. Tennent-Brown, BSc, DipSc, BVSc, MS[a,*],
Ashleigh V. Morrice, BSc, DVM[a], Stephen Reed, DVM[b]

KEYWORDS

• Neonatal encephalopathy • Neurosteroids • Allopregnanolone • Progestagens

KEY POINTS

- Neonatal encephalopathy (neonatal maladjustment syndrome, hypoxic-ischemic encephalopathy) is the most common neurologic condition affecting newborn foals and shares similarities with perinatal asphyxia syndrome of human infants.
- In many cases of neonatal encephalopathy there is no obvious episode of acute or chronic hypoxia and other mechanisms likely play a role in the pathogenesis.
- The role of neurosteroids in neonatal encephalopathy has been investigated and increased concentrations of neuroactive progestagens are found in affected foals; whether these molecules are protective, as has been suggested, or play a role in the pathogenesis is unknown.
- Neurologic diseases other than neonatal encephalopathy affect foals occasionally and should be considered when evaluating sick foals with clinical signs of neurologic dysfunction.

INTRODUCTION

Neonatal encephalopathy (NE; neonatal maladjustment syndrome [NMS], hypoxic-ischemic encephalopathy [HIE]) is the most common disease affecting the central nervous system (CNS) of equine neonates. The condition has often been compared with perinatal asphyxia syndrome (PAS) in human infants but it seems likely that oxygen deprivation during gestation or parturition is not the only mechanism by which NE occurs. In a subset of foals, NE might occur as a result of an inflammatory insult or from

Funding Sources: None.
Conflicts of Interest: None.
[a] Equine Centre, Faculty of Veterinary and Agricultural Sciences, The University of Melbourne, 250 Princess Highway, Werribee, Victoria 3030, Australia; [b] Rood and Riddle Equine hospital, 2150 Georgetown Road, Lexington, KY 40511, USA
* Corresponding author.
E-mail address: brett.tennent@unimelb.edu.au

Vet Clin Equine 31 (2015) 587–600
http://dx.doi.org/10.1016/j.cveq.2015.08.002 **vetequine.theclinics.com**
0749-0739/15/$ – see front matter

failure to make the transition from intrauterine to extrauterine life. Several recent studies have focused on the role of a group of molecules termed neurosteroids that influence alertness and arousal of the fetus and seem to be important in the onset of consciousness in neonates. The bulk of this article discusses aspects of the endocrine changes that occur at birth and the role that these changes might play in NE. Other conditions affecting the equine neonatal brain are covered only briefly and interested readers are directed to an excellent recent review.[1]

CENTRAL NERVOUS SYSTEM DEVELOPMENT IN THE FETUS

The Hypothalamic-Pituitary-Adrenal Axis and the Transition from Intrauterine to Extrauterine Life

The fetal hypothalamic-pituitary-adrenal (HPA) axis plays a pivotal role in the transition from intrauterine to extrauterine life (recently reviewed by Fowden and colleagues,[2] 2012). Furthermore, the pattern of cortisol and steroid hormone secretion by the fetal adrenal gland is an important signal in initiating labor. Before 290 days of gestation, fetal pituitary secretion of adrenocorticotropic hormone is low and the adrenal glands produce mainly pregnenolone (a steroid hormone precursor synthesized from cholesterol). Fetal pregnenolone is thought to be the main precursor for the progestagens synthesized by the uteroplacental tissues. These progestagens are responsible for maintaining the uterus in a quiescent state if there is increased stretching by the fetus.[3–6] Fetal HPA axis activity increases and is accompanied by adrenal gland development after 300 days of gestation. Very late in gestation, in just the last 24 to 48 hours before parturition, the fetal adrenal switches from pregnenolone production to cortisol production. Fetal pregnenolone concentrations consequently decrease; removal of this precursor results in a sharp decrease in maternal progestagen concentration and an increase in uterine activity. The concomitant increase in fetal cortisol concentration facilitates maturation of a wide range of body systems that are essential to extrauterine life, including the respiratory, gastrointestinal, hepatic, and renal systems.[7,8] Normal HPA axis development and function are disrupted by both prematurity and sepsis, and the degree of disruption seems to have an important influence on the occurrence of disease and survival of affected neonates.[9–12]

Neurosteroids in Central Nervous System Development and Function

The neurosteroids are a collection of steroid hormones synthesized from cholesterol or other circulating steroids by enzymes located within the CNS.[13] These molecules are thought to be important in the transition to extrauterine life and the onset of consciousness[14,15] but also have roles in neurologic function and disease in the fetus, neonate, and adult.[13] As with traditional steroid hormones, the neurosteroids can modulate gene expression; however, they also have important and much more rapid actions at several neurotransmitter receptors, including the gamma-aminobutyric acid (GABA) A and *N*-methyl-D-aspartate (NMDA) receptors.[13]

GABA is the most important inhibitory neurotransmitter within the mammalian CNS and the $GABA_A$ receptors are a family of ligand-gated anion channels.[16] There are approximately 20 to 30 isoforms of the $GABA_A$ receptor with distinct physiologic properties.[17] Combined with differing regional expression of the $GABA_A$ receptors throughout the CNS, this results in a high degree of specificity.[17] The neurosteroids probably do not function by themselves at the $GABA_A$ receptor but potentiate the action of GABA (and possibly other ligands) at the receptor.[13] Neurosteroid binding at the $GABA_A$ receptor generally has a depressant effect on the CNS as a result of increased GABAergic inhibition and anion (chloride ion) influx.