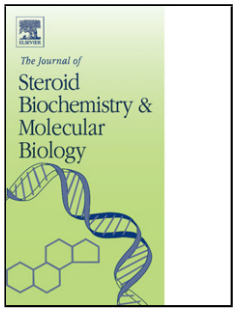

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Loss of neurosteroid-mediated protection following stress during fetal life

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Highlights

Elevated neurosteroids during pregnancy have major protective and neurotrophic roles in the fetal brain

Preterm birth and maternal stress during pregnancy may deprive the fetus of adequate neurosteroid-mediated support

Neurosteroid therapy following preterm birth and compromised pregnancy may improve long-term outcomes

Abstract

Elevated levels of neurosteroids during late gestation protect the fetal brain from hypoxia/ischaemia and promote neurodevelopment. Suppression of allopregnanolone production during pregnancy leads to the onset of seizure-like activity and potentiates hypoxia-induced brain injury. Markers of myelination are reduced and astrocyte activation is increased. The placenta has a key role in maintaining allopregnanolone concentrations in the fetal circulation and brain during gestation and levels decline markedly after both normal and preterm birth. This leads to the preterm neonate developing in a neurosteroid deficient environment between delivery and term equivalence. The expression of 5α-reductases is also lower in the fetus prior to term. These deficiencies in neurosteroid exposure may contribute to the increase in incidence of the adverse patterns of behaviour seen in children that are born preterm. Repeated exposure to glucocorticoid stimulation suppresses 5α-reductase expression and allopregnanolone levels in the fetus and results in reduced myelination. Both fetal growth restriction and prenatal maternal stress lead to increased cortisol concentrations in the maternal and fetal circulation. Prenatal stress results in reduced expression of key $GABA_A$