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Review

Neuroactive steroids in pregnancy: Key regulatory and protective roles in the foetal brain

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ABSTRACT

Neuroactive steroid concentrations are remarkably high in the foetal brain during late gestation. These concentrations are maintained by placental progesterone synthesis and the interaction of enzymes in the placenta and foetal brain. 5α-Pregnane-3α-ol-20-one (allopregnanolone) is a key neuroactive steroid during foetal life, although other 3α-hydroxy-pregnanes may make an additional contribution to neuroactive steroid action. Allopregnanolone modulates GABAergic inhibition to maintain a suppressive action on the foetal brain during late gestation. This action suppresses foetal behaviour and maintains the appropriate balance of foetal sleep-like behaviours, which in turn are important to normal neurodevelopment. Neuroactive steroid-induced suppression of excitability has a key role in protecting the foetal brain from acute hypoxia/ischaemia insults. Hypoxia-induced brain injury is markedly increased if neuroactive steroid levels are suppressed and there is increased seizure activity. There is also a rapid increase in allopregnanolone synthesis and hence levels in response to acute stress that acts as an endogenous protective mechanism. Allopregnanolone has a trophic role in regulating development, maintaining normal levels of apoptosis and increasing myelination during late gestation in the brain. In contrast, chronic foetal stressors, including intrauterine growth restriction, do not increase neuroactive steroid levels in the brain and exposure to repeated synthetic corticosteroids reduce neuroactive steroid levels. The reduced availability of neuroactive steroids may contribute to the adverse effects of chronic stressors on the foetal and newborn brain. Preterm birth also deprives the foetus of neuroactive steroid mediated protection and may increase vulnerability to brain injury and suboptimal development. These finding suggest replacement therapies should be explored.

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Contents

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1. Introduction

In species that have long gestations such as the human, sheep and guinea pigs the placenta synthesises considerable amounts of progesterone over the last half of gestation [1]. Concentrations are markedly higher compared to non-pregnant levels and generally rise with advancing gestation. The production of progesterone by the placenta, and potentially the corpus lutuem in some species, has a key role in providing precursors for the synthesis of neuroactive steroids. This precursor production makes a major contribution to the synthesis of allopregnanolone (5α-pregnane-3α-ol-20-one) in the foetal periphery and brain, and leads to relatively high levels of this neuroactive steroid in the foetal brain during pregnancy compared to after birth [2]. Examination of the mechanisms controlling neuroactive steroid production in the foetus highlights the key role of interactions between the placenta and foetal brain in long gestation species (Fig. 1). Neuroactive steroids have a major influence over CNS activity and are essential for growth and neuronal and glial cell survival [3,4]. Progesterone has potent repair-promoting actions following traumatic brain injury in adults [5,6] and most of this action results from its metabolism to 5α-reduced metabolites including allopregnanolone [7]. Placental precursor production and the high levels reached in the foetal brain suggest allopregnanolone is the most important protective steroid [2]. Allopregnanolone has an essential role in the suppression of excitability and reducing potentially damaging seizures [8]. Thus reduction in synthesis of allopregnanolone due to compromises during pregnancy may increase the vulnerability of foetal brain to seizure-induced damage. Studies in adult animals indicate that neuroactive steroids have an important trophic role in the brain and may contribute to repair processes after brain injury enhancing myelination and reducing apoptotic processes [9,10]. Our recent studies suggest this is also the case in the foetus. We found the suppression of allopregnanolone synthesis caused increased cell death in the brain and resulted in delayed myelination of the white matter tracts [11,12]. Changes in glial cell activation have also been identified and this may suggest changes to the maturation of oligodendrocytes [4]. These findings further support the importance of allopregnanolone to the developing brain and suggest that exposure to normal neuroactive steroid levels is critical. The loss of such support after premature birth may markedly contribute to neuromorbidity even if there is only a moderate degree of prematurity.

Stressful events during pregnancy, especially those leading to transient hypoxia/ischaemia stimulate the production of allopregnanolone in the brain providing further protection and trophic support [13]. Much of this protection is lost after birth when allopregnanolone levels fall, however, the term newborn can produce neuroactive steroid responses that are neuroprotective [14]. Thus, rising allopregnanolone levels after lipopolysaccharide treatment show that the term newborn is able to increase neuroactive steroids in the brain in response to inflammatory stress, but not to the extent seen during foetal life. Premature birth and other pregnancy compromises lead to marked changes in allopregnanolone levels in the brain and therefore the exposure to adverse conditions without the benefit of neuroactive steroid-mediated protection [8]. Complications of pregnancy, including placental insufficiency, foetal growth restriction and chronic foetal hypoxaemia, are all associated with a higher risk for adverse outcomes including brain injury. These conditions may result in marked morbidity including cerebral palsies or less severe damage that may become apparent with advancing age [15]. It is now well-accepted that many of the behavioural problems of childhood and older ages arise during pregnancy [16,17]. Reduced neuroactive steroid levels in the foetal brain may contribute to these adverse outcomes [11,12].

The rise in cortisol levels that is associated with stress in pregnancy has been implicated in adverse outcome [18]. We have reported that synthetic corticosteroid administration to the foetus, supresses neuroactive steroid synthetic enzyme expression, and a similar suppression may occur following stress-induced increases in cortisol levels in the foetus [19]. The interaction between neuroactive steroid pathways and glucocorticoid levels may have a major impact on the developing brain. Furthermore some glucocorticoids and their metabolites may be neuroactive [20], however, there is little information on the potential roles of these metabolites in stress-induced pathologies or on interactions between the placenta and foetal brain.

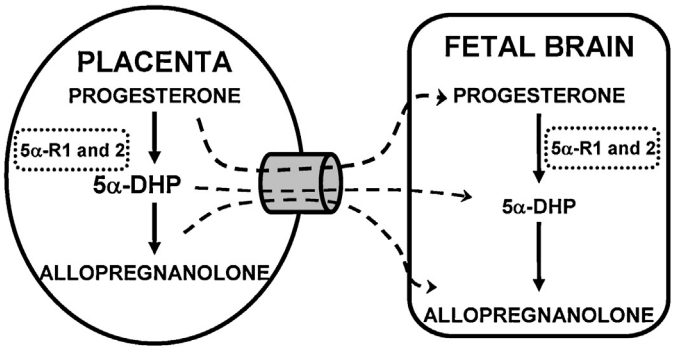

Fig. 1. Pathways contributing to allopregnanolone levels in foetal brain. The placenta may contribute progesterone, precursor metabolites and/or allopregnanolone directly to the brain. Both 5α-reductases-1 and -2 are expressed in the placenta and foetal brain, although 5α-reductase-2 may make the major contribution to activity in the foetal brain. 5α-R1: 5α-reductase-1; 5α-R2: 5α-reductase-2, and 5α-DHP: 5α-dihydroprogesteron.

2. Regulation of neurosteroid concentrations in the foetal and neonatal brain

Progesterone and allopregnanolone are the most important neuroactive steroids present during pregnancy as they are found in remarkably high concentrations in the foetal circulation and brain, respectively [2]. Allopregnanolone levels in the foetal brain are regulated by intimate interactions between the placenta and brain itself and in the foetal sheep reach up to 400 pmol/g in some regions [2]. These levels far exceed those seen after birth 20–40 pmol/g or in adults and are higher than concentrations in the foetal sheep circulation during late pregnancy (80–100 nmol/L). Allopregnanolone levels are also elevated in human maternal [21] and foetal circulations [22], however concentrations reached in the human foetal brain are not available. The placenta produces substantial amounts of pregnenolone and progesterone during pregnancy with production far exceeding cyclic production in non-pregnancy [23]. This steroid production results in the entry of large amounts of progesterone into the maternal circulation where it not only maintains uterine quiescence and influences maternal immune function, but also influences maternal CNS activity with improvements in seizure threshold and reduced anxiety [24]. This is consistent with the metabolism of progesterone to neuroactive steroids and elevated levels of $GABA_A$ receptor agonist steroids some of which readily cross the placenta [25]. The effects on excitability are lost at birth with the removal of the placenta and decline in neuroactive steroid levels in the plasma [21,26]. Placental steroidogenesis markedly influences foetal progesterone levels, however in the sheep, the placenta metabolises much to the progesterone produced and consequently concentrations in the foetal circulation are less than those in the maternal circulation [27]. Alternative in human pregnancy more progesterone reaches foetus un-metabolised and levels in the foetal umbilical vein are considerably higher than those in the material circulation [28–31]. Both the human and sheep