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Evidence for adverse effect of perinatal glucocorticoid use on the developing brain

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The use of glucocorticoids (GCs) in the perinatal period is suspected of being associated with adverse effects on long-term neurodevelopmental outcomes for preterm infants. Repeated administration of antenatal GCs to mothers at risk of preterm birth may adversely affect fetal growth and head circumference. Fetal exposure to excess GCs during critical periods of brain development may profoundly modify the limbic system (primarily the hippocampus), resulting in long-term effects on cognition, behavior, memory, co-ordination of the autonomic nervous system, and regulation of the endocrine system later in adult life. Postnatal GC treatment for chronic lung disease in premature infants, particularly involving the use of dexamethasone, has been shown to induce neurodevelopmental impairment and increases the risk of cerebral palsy. In contrast to studies involving postnatal dexamethasone, long-term follow-up studies for hydrocortisone therapy have not revealed adverse effects on neurodevelopmental outcomes. In experimental studies on animals, GCs has been shown to impair neurogenesis, and induce neuronal apoptosis in the immature brains of newborn animals. A recent study has demonstrated that dexamethasone-induced hypomyelination may result from the apoptotic degeneration of oligodendrocyte progenitors in the immature brain. Thus, based on clinical and experimental studies, there is enough evidence to advice caution regarding the use of GCs in the perinatal period; and moreover, the potential long-term effects of GCs on brain development need to be determined.

Key words: Glucocorticoids, Dexamethasone, Hydrocortisone, Fetus, Newborn infant

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Introduction

Although glucocorticoids have been widely used in the perinatal period, their use is suspected of being associated with adverse effects on fetal growth and long-term neurodevelopmental outcomes in preterm infants[1-5]. Since the trials conducted by Liggins and Howie in 1972[6], many observational and controlled studies have reported that antenatal administration of glucocorticoids (GCs) to mothers at risk of preterm birth decreases the severity of respiratory distress syndrome and improves the survival of preterm infants[6-10]. However, repeated courses of antenatal GCs may be associated with reduced fetal brain growth and long-term neurodevelopmental impairment[10-17]. Several studies of systematic reviews and meta-analyses have shown that postnatal use of GCs to prevent or treat chronic lung disease (CLD) in preterm infants may facilitate extubation and decrease the incidence of bronchopulmonary dysplasia (BPD), but have found that it increases the risk of neurodevelopmental impairment and cerebral palsy (CP), particularly in infants treated with dexamethasone within the first week of life[2-5,18-24]. In addition, fetal exposure to excessive GCs may induce a significant change in the hypothalamic-pituitary adrenal (HPA) axis[25-29]. Studies using magnetic resonance imaging (MRI) have demonstrated a significant reduction in brain tissue volumes in infants treated with GCs in the perinatal period[24,30-34]. The

purpose of this review was to evaluate clinical and experimental evidence for the adverse impact of GCs on the developing brain.

Clinical evidence for adverse effects of antenatal GCs on the developing brain

A relatively brief course of antenatal GCs administration (dexamethasone or betamethasone) improves survival and appears to protect against brain damage[2,10,35-37]. In clinical trials and observational studies, antenatal administration of GCs has been associated with a decreased risk of intraventricular hemorrhage and CP in preterm infants, and confers protection against periventricular leukomalacia[35-37]. The protective effect on the white matter appears to be greater among infants who show evidence of a fetal inflammatory response, such as chorioamnionitis[36,37]. In one retrospective study, antenatal exposure to betamethasone, but not dexamethasone, was associated with the decreased risk of cystic periventricular leukomalacia in premature infants of 24 to 31 weeks gestation[37]. With regard to neurodevelopmental outcomes, a single course of antenatal GCs is generally thought to be beneficial[14,38-43]. However, the use of repeated courses of antenatal GCs has been more controversial, despite some evidence for neonatal benefit if the mother remains at risk of preterm labor [29]. Several nonrandomized studies concerning repeated courses of antenatal GCs have reported adverse effects on fetal growth and head circumference, suppression of the fetal HPA axis, and abnormal neurodevelopment[13,27,28]. Repeated betamethasone injections, given to the mother at weekly intervals, have resulted in improvements in postnatal lung function, but also a reduction in birth weights[42]. In studies using volumetric MRI, repeated antenatal GC treatments have been associated with a decreases in brain surface area, in the whole cortex convolution index, and in a measure of cortical surface complexity in preterm infants[43]. A study by the Australasian Collaborative Trial of Repeat Doses of Steroids reported that repeated administration of antenatal GCs to mothers at risk of preterm birth reduced neonatal morbidity, without changing either survival free of major neurosensory disability or body size at 2 years of ages, although *z*-scores for weight and head circumference were lower at birth in the repeated-dose group compared with the single-dose group[16]. One systematic review reported that repeated administration of betamethasone weekly or biweekly restricted intrauterine growth, which has raised concerns about long-term consequences on neurodevelopment and metabolism[14].

Endogenous GCs are essential for many aspects of normal brain development. However, dexamethasone and betamethasone readily cross the placental barrier, potentially exposing the fetus to excess GCs[29], which can suppress the HPA axis and endogenous cortisol production[27-29,33]. Overexposure of the fetus to corticosteroids by using synthetic GCs during certain stages of pregnancy can profoundly affect the development of the neuroendocrine system which may lead to life-long effects on endocrine, behavioral, emotional, and cognitive function. These life-long effects on neuroendocrine function are associated with increased risks of developing a wide range of metabolic, cardiovascular, and brain disorders in later life[25,26].

In summary, a single course of antenatal GCs administered to mothers at risk of premature labor has major benefits for infants born before 34 weeks gestation[6-10,35-41]. However, there is limited information available on the long-term effects of antenatal GCs on neurodevelopment in humans. Repeated courses of antenatal CGs may be associated with reduced birth weight and fetal head growth. Fetal exposure to excess GCs can affect the development of the neuroendocrine system, potentially leading to life-long effects on endocrine, behavior, emotional, and cognitive function. More studies including long-term follow-up of exposed children are needed to confirm the efficacy and safety of antenatal GCs use, especially of repeated courses of treatment.

Clinical evidence for adverse effects of postnatal GCs on the developing brain

Since the first report in 1974, a number of studies have showed that use of postnatal GCs to treat or prevent CLD increases the risk of neurodevelopmental disability and CP in preterm infants[19-23,44-67]. Among systemically administered postnatal GCs, dexamethasone has been extensively studied and has proven to be effective in the management of BPD because of its anti-inflammatory effects[45]. Dexamethasone is a potent, long-acting steroid with exclusively glucocorticoid effects. Its use has been studied during the early (<7 days), moderately early (7–14 days) and late/delayed (>14 days) postnatal periods at doses ranging from 0.1 mg/kg/day to 0.5 mg/kg/day, and durations ranging from 3 to 42 days[2,4,5,21,44-63]. In recent systematic meta-analysis reviews, early postnatal treatment with dexamethasone within the first week of birth was shown to induce neurodevelopmental disability and increase the risk of CP, despite its short-term beneficial effects on the lung function[21]. In contrast, one extensive systematic review showed that treatment with dexamethasone after the first week of postnatal life may actually reduce mortality rates or the incidence of long-term neurodevelopmental disability although long-term follow-up data remains limited[55]. In addition, it has been suggested that high dosage (0.5 mg/kg/day) and long duration of treatment may be the factors responsible for delays in brain growth and poor neurodevelopmental outcomes[64]. Follow-up data reported by Wilson-Costello et al.[65] in 2009 has suggested that every for every 1 mg/kg increase in the cumulative dose of dexamethasone, the risk of developing disabling CP increased by

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40% at every gestational age. However, in a systematic review of placebo-controlled trials, Onland et al.[66] reported that higher cumulative dexamethasone doses after the first week of life decreased the risk of BPD without increasing the risk of neurodevelopmental disability in ventilated preterm infants, and had no effect on neurodevelopmental outcomes after the third week of life. The severity of CLD can modify the effect of steroids on CP. One meta-analysis by Doyle et al.[51] showed that postnatal treatment with GCs increased the likelihood of death or CP in infants whose risk of CLD was below 35%, but reduced the likelihood of death or CP if the risk of CLD exceeded 65%. The results of randomized controlled trials (RCTs) that have been performed to evaluate long-term neurodevelopmental outcomes from postnatal dexamethasone use are summarized in Table 1. The results vary. Some studies did not reveal adverse effects on neurodevelopmental outcomes at various ages. In particular, the results from two RCTs using lower doses of dexamethasone (0.15 mg/kg/day for 3 days, then tapering over 7 days) did not show a significant increase in CP and neurodevelopmental impairment when compared with placebo[23,58].

Hydrocortisone is the second most commonly used postnatal GC in premature infants. Extremely premature infants have developmental immaturity of the HPA axis during the first few weeks of life, predisposing them to relative adrenal insufficiency and inadequate anti-inflammatorty defenses against acute illness[68]. Consequently, early physiological replacement of cortisol may be needed in extremely premature infants[68]. Retrospective studies and RCTs of early hydrocortisone replacement for CLD within the first week of life have been performed on the basis of this relative adrenal insufficiency[69-80]. Hydrocortisone is also being used increasingly for the treatment or prevention of vasopressor-resistant hypotension in extremely premature infants[68]. In contrast to postnatal dexamethasone, the long-term follow-up studies for hydrocortisone therapy have not revealed adverse effects on neurodevelopmental outcomes [79,80]. In a retrospective study, van der Heide-Jalving et al.[79] reported that no differences in neurodevelopment outcomes at 5–7 years of age were found between the hydrocortisone-treated group (n=25) and control subjects (n=25). Watterberg et al.[73] evaluated a total of 252 infants from 291 survivors with birth weights of 500–999 g at 18 to 22 months corrected age. Low doses of hydrocortisone treatment (1 mg/kg/day for 12 days, followed by 0.5 mg/kg/day for 3 days) was not associated with increased rates of developmental delay and CP in surviving infants[73]. However, hydrocortisone significantly increased the risks of spontaneous gastro-intestinal perforation[69]. This complication was also observed with early dexamethasone treatment and may result from interactions with indomethacin/ibuprofen[23,69]. Low (1 mg/kg/day) or relatively high doses (3–6 mg/kg/day) of hydrocortisone treatment in neonates has had no discernible effect on brain lesions and total or regional brain volumes measured using MRI in short-term or long-term follow-up studies continued until school age[31]. In a recent meta-analysis of eight RCTs enrolling a total of 880 infants, postnatal treatment with low (1–2 mg/kg/day) or high dose (3–6 mg/kg/day) hydrocortisone has not shown any adverse effects on neurodevelopment[22]. This study has demonstrated that there is little evidence for a direct effect of hydrocortisone on the rates of BPD, mortality, or the combined outcome of BPD or mortality[22]. The results of long-term outcome studies of postnatal hydrocortisone use are summarized in Table 2.

There are several possible explanations for these differences between the effects of dexamethasone and hydrocortisone on brain growth and neurodevelopment[45,81,82]. Hydrocortisone has almost equal glucocorticoid and mineralocorticoid actions, and its half-life is only 8 hours. When compared to hydrocortisone, dexamethasone has exclusive glucocorticoids action, is 25–50 times more potent, and its half-life is 36–54 hours[45]. High-dose dexamethasone (0.5 mg/kg/day) is equivalent to at least a 15–20 mg/kg/day dose of hydrocortisone, far higher than the range of doses of hydrocortisone given in the studies discussed above (1–6 mg/kg/day). Even low-dose dexamthasone (0.1–0.15 mg/kg/day) may be equivalent to a 3–6 mg/kg/day dose of hydrocortisone, but has a longer half-life[45,46,83]. Therefore, dexamethasone may have a much higher relative potency than hydrocortisone, predisposing recipients to an increased risk of neurodevelopmental disability. Dissimilar effects of these two agents on the hippocampus have also been reported in animal studies. The hippocampus contains high densities of both mineralocorticoid and glucocorticoid receptors (GRs)[81,82]. Dexamethasone, which binds only to GRs, has been shown to induce neurodegeneration within the hippocampus[84,85]. In humans, neonatal treatment with dexamethasone, but not hydrocortisone, has been shown to alter hippocampal synaptic plasticity and associative memory formation in later life[1]. Dexamethasone exposure has also been linked to decreased hippocampal volume, but cohort studies of infants treated with hydrocortisone have not revealed a decrease in hippocampal volume[31,33,34,70,71].

In summary, when considering postnatal GCs use, the least toxic GC should be given at the lowest effective dose for the shortest possible time[75]. Use of postnatal CGs should be limited to those who are expected to need prolonged ventilation, and have a higher risk of development of CLD[2,4]. Particularly, dexamethasone should not be given in the first week of life unless the treatment is life-saving, and after the second week of life, its use should be restricted to those infants whose ventilator requirements suggest that they are at high risk of developing severe CLD[5]. The follow-up studies tend to favor hydrocortisone as a safer alternative to dexamethasone. However, follow-up studies on postnatal dexamethasone treatment were placebo-controlled randomized studies, whereas most of hydrocortisone follow-up studies were retrospective cohort studies (Tables 1, 2). The use hydrocortisone as a safer alternative to dexamethasone requires

Table 1. Summary for neurodevelopmental follow-up outcomes of randomized controlled trials of postnatal dexamethasone for chronic lung disease in premature infants

Study	Type of study	Enrolled infants	Start day of treatment	Dosage and regimen	Total dose of DEX	Follow-up
Early (<7 days) treatment						
Stark et al.[67]	Randomized controlled trial	DEX, n=111; control, n=109, BW 501–1,000 g, treatment with mechanical ventilation within 12 hours after birth	<24 hours after birth	0.15 mg/kg/day for 3 days, then tapered over 7 days	0.89 mg/kg	n=102 in the DEX group and 92 in the control followed up at 18–22 months of corrected age. No difference of combined death or NDI was between the DEX and control groups
Romagnoli et al.[59]	Randomized controlled trial	DEX, n=25; control, n=25, BW <1,250 g, GA <32 weeks, ventilator- and oxygen-dependent at 72 hours of life	On the 4th day of life	0.5 mg/kg/day for the first 3 days, 0.25 mg/kg/day the next 3 days, and 0.125 mg/kg/day on the seventh day	2.375 mg/kg	n=45 surviving infants (22 untreated and 23 treated) completed the 3-year follow-up. No differences were detected between DEX and control groups in regard to incidence of major cranial ultrasound abnormalities, cerebral palsy, major neurosensory impairment or IQ scores and distribution.
Wilson et al.[63]	Randomized controlled trial	DEX, early (< 3 days, n=135) versus delayed selective (>15 days, n=150), GA <30 weeks with FiO_2 >0.3	Early (<3 days after birth), delayed selective (>15 days after birth)	Early <3 days of age, 0.5 mg/kg/day for 3 days, then tapered for a total 12 days, late selective on 15-day age, inhaled early or late budesonide	2.7 mg/kg	n=61 followed up at 7 years of age. No significant difference of cognitive, ability, behavior, CP and combined death or CP
Yeh et al.[19]	Randomized controlled trial	DEX, n=132; control, n=130, BW 500–1,999 g, severe respiratory distress syndrome with mechanical ventilation within 6 hours after birth	<12 hours after birth	0.25 mg /kg, intravenously every 12 hours, from day 1 through day 7, 0.12 mg /kg from day 8 through day 14, 0.05 mg /kg from day 15 through day 21, and 0.02 mg/kg from day 22 through day 28	6.16 mg/kg	n=146 (72 in the DEX and 74 in the control group) followed up at school age. The frequency of clinically significant disabilities was higher among children in the DEX group than among controls (39% versus 22 %, P=0.04).
Moderated or late (≥7 days of age) treatment						
McEvoy et al.[56]	Randomized controlled trial	High dose DEX, n=29, low dose DEX, n=33	At 7–21 days of age	High versus low dose (0.5 mg/kg versus 0.2 mg/kg tapered over 7 days)	2.35 mg/kg vs. 1 mg/kg	n=39 followed up at 9–15 months of corrected age. No significant difference of MDI <70; high (24%) versus low (17%), and CP; high (10%) versus low (11%).
Armstrong et al.[57]	Randomized controlled trial	Seventy six babies were enrolled. BW ≤1,250 g, ventilated at ≥15 cycles/min at 7 days of age	On the 7th day of age	5 mg/kg/day over 42 days tapering versus 3-day pulse	4.0 mg/kg	n=64 followed up at 18 months of corrected age. No significant difference of neurodevelopmental disability (34% versus 31%).
Doyle et al.[58]	Randomized controlled trial	DEX, n=70; control, n=35, GA <28 weeks, BW <1,000 g, ventilated after 7 days of age	After 7 days of age	0.15 mg/kg/day tapered over 10 days versus placebo	0.89 mg/kg	n=58 followed up at 2 years of age. No significant difference of death or major disability (46% versus 43%), and death or CP (23% versus 37%).
O'shea et al.[60]	Randomized controlled trial	DEX, n=51; control, n=61, BW<1,501 g, age between 15 and 25 days, <10% decrease in ventilator settings for the previous 24 hours and fraction of inspired oxygen ≥0.3	At 15 to 24 days of age	0.5 mg/kg/day tapered over 42 days versus placebo	4.0 mg/kg	n=84 followed up at 4–11 years of age. Significantly higher prevalence of major neurodevelopmental impairment and CP.
Gross et al.[61]	Randomized controlled trial	n=36, BW≤1,250 g and GA≤30 weeks, dependent on mechanical ventilation at 2 weeks of age	On the 14th day of life	0.5 mg/kg tapered over 42 days course versus 18 days course versus placebo	4.0 mg/kg	n=22 survived and followed to 15 years age. 42 days course; significantly greater in intact survival (IQ >70, normal NE, regular school education) than 18 days course and placebo (62% versus 25% versus 18%, P<0.05)

DEX, dexamethasone; BW, birth weight; GA, gestational age; NDI, neurodevelopmental index; CP, cerebral palsy; IQ, intelligence quotient; MDI, mental developmental index; NE, neurologic examination.

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Table 2. Summary for neurodevelopmental follow-up outcomes of retrospective and prospective clinical trials of postnatal hydrocortisone in premature infants

Study	Type of study	Enrolled infants	Start day of treatment	Dosage and regimen	Total dose of HC	Follow-up
van der Heide-Jalving et al.[79]	Retrospective, matched control	HC, n=25; control, n=25	Mean, 2.1 weeks of postnatal age	Tapering course of 5 to 1 mg/kg/day over 22 days	72.5 mg/kg	No differences between neonatal HC-treated children and controls on neurodevelopmental outcome at 5-7 years of age.
Karemaker, et al.[80]	Retrospective, cohort	HC, n=52; DEX, n=46; control, n=43	Mean, 14 days of age	HC; starting with 5 mg/kg/day and tapering off to 1 mg/kg/day over a 22 days DEX; starting with 0.5 mg/kg/day and tapering to 0.1 mg/kg/day over 21 days	72.5 mg/kg	At school age, poorer neuromotor development in DEX than control group. The HC group did not differ from control.
Lodygensky et al.[70]	Retrospective cohort	HC, n=25; control, n=35	Median, 18 days of age	Starting with 5 mg/kg/day and tapered over 3 weeks	72.5 mg/kg	At 8 years, no difference in quantitative 3-dimensional MRI volumes of cerebral tissues and WISC scores
Watterberg et al.[73]	Randomized, placebo controlled	HC, n=126; control, n=126	<12–48 hours of age	1 mg/kg/day for 12 days, followed by 0.5 mg/kg/day for 3 days	13.5 mg/kg	At 18–22 months of corrected age, hydrocortisone-treated patients were less likely to have a MDI <70 among infants not exposed to chorioamnionitis
Rademaker et al.[31]	Retrospective cohort	HC, n=62; control, n=164	Mean, 19 days of age	Starting dose of 5 mg/kg/day, divided into 4 doses for 1 week, followed by a tapering course of 3, 2, and 1 dose each for 5 days	70.0 mg/kg	At school age, adjusted mean IQ, Visual Motor Integration test, and memory test results were the same in the hydrocortisone-treated group and the non–steroid-treated group. Motor function and incidence of cerebral palsy in both groups was not different.
Yamasaki et al.[78]	Prospective case control	Three groups; CLD (+) and treated with HC (n=24); CLD (+) but not treated with HC (n=40); CLD (–) and not treated (n=46)	Mean, 21.2 days of age	1–2 mg at 12–48 hours intervals if indicated	4.0 mg/kg	At the corrected age of 18 months, no significant differences among the three groups in terms of growth and neurodevelopmental quotient.

HC, hydrocortisone; DEX, dexamethasone; MRI, magnetic resonance image; WISC, Wechsler Intelligence Scales for Children; MDI, mental developmental index; IQ, intelligence quotient; CP, cerebral palsy; CLD, chronic lung disease.

more evidence to confirm that hydrocortisone is safer in term of long-term neurological outcomes.

Experimental evidences for adverse effects of GCs on the developing brain

Corticosteroids are essential for normal brain development. Two types of corticosteroid receptor: mineralocorticoid receptors (MRs) and GRs[81]. MRs are predominantly expressed in the limbic structures (primarily the hippocampus), whereas GRs are more diffusely distributed with highest levels in the limbic system, hypothalamic paraventricular nucleus, and the cerebral cortex. Endogenous GC (cortisol in humans, corticosterone in rats) binds to MRs with a higher affinity than to GRs[1,81,82]. Under basal conditions, MRs are predominantly occupied, while, in the stressed condition, in which the level of cortisol is increased, the occupation of GRs increases[1,82]. Within the developing brain, the limbic system is particularly sensitive to endogenous and exogenous GCs[82]. A study using guinea pigs has demonstrated that fetal exposure to exogenous GCs modified the expression of GR and MR mRNA in the hippocampus and dentate gyrus[84]. Synthetic GCs (dexamethasone and betamethasone) bind predominantly to the GRs. Therefore, the impact of exogenous synthetic GCs on brain development is likely mediated by modification of GR expression in the brain, and may be dependent on the level of expression of GRs at the time of exposure[1,26].

Changes in the expression of GRs and MRs in the hippocampus can result in long-term modification of the HPA axis[25,26]. Fetal exposure to exogenous GCs during the critical periods of brain development may exert a profound influence on the limbic system (primarily the hippocampus), resulting in long-term changes in cognition, behavior, memory, co-ordination of the autonomic nervous system, and regulation of a number of endocrine system functions later in adult life[26,28,29]. Exposure to synthetic GCs in utero results in hyperactivity of the HPA axis in adults, which will have a long-term impact on health[24-29]. There is growing evidence that prenatal exposure to GCs may be linked to the premature onset of cardiovascular and metabolic diseases, such as hypertension and diabetes[26,28,29].

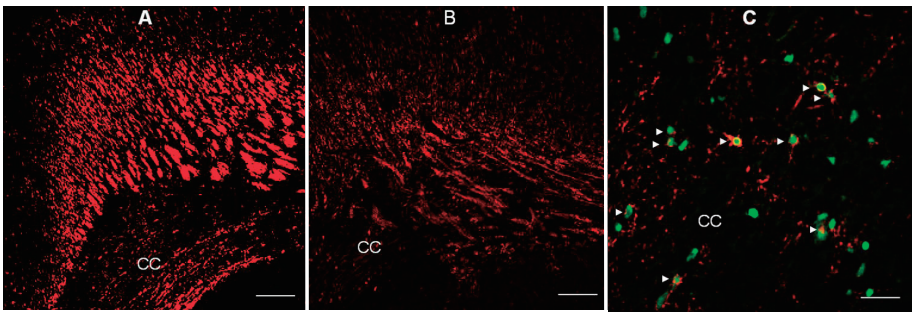

Fig. 1. Immunofluorescent staining for myelin basic protein (MBP) in the forebrain of rats administered saline ((A, ×100, 100 μm) and dexamethasone (B, ×100, 100 μm) at P14, and confocal laser microscopic images of the corpus callosum of rats administered dexamethasone (C, ×400, 25 μm), double-stained on P5 using TUNEL and O4 antibody. Repeated administration of dexamethasone (0.5 mg/kg/day) from P1 to P5 reduced the immunofluorescent expression of MBP at P14 in the forebrain (B), compared with administration of saline (A). The expression of MBP decreased in the corpus callosum (CC), and its overlying supracallosal radiation. Many O4–positive cells with pyknotic TUNEL-positive nuclei (►) indicative of apoptosis were observed in the corpus callosum of rats administered dexamethasone.

Animal studies have shown that GCs, especially dexamethasone, impaired neurogenesis and induced neuronal apoptosis[85,86]. Repeated administration of dexamethasone to neonatal rats has resulted in dose-dependent decrease in the neurogenesis in the subventricular zone, subgranular zone and cortex, and also resulted in a decrease in the brain weight[86]. Exposure of the immature mouse brain to clinically relevant doses of GCs has been shown to cause apoptosis of neural progenitor cells in the external granular cell layer of the developing mouse cerebellum, and leads to permanent decreases in the number of cerebellar neurons[87,88]. Dexamethasone treatment in neonatal rats has led to significantly decreased brain weights and increased cleaved casepase-3 levels in the cortex, thalamus, hippocampus, cerebellum, dentate gyrus and subventricular zone[89]. These findings suggest that the decrease in brain weight and the accompanying neurodevelopmental impairment may be due to impaired neurogenesis and/or degeneration of neurons by GCs.

The involvement of corticosteroids in myelin biosynthetic pathways is well known[89,90]. Dexamethasone affects myelin basic protein (MBP) synthesis by modulating gene expression, or by acting on GRs[91]. Repeated administration of dexamethasone has been shown to adversely affect the myelination of the developing rat brain, and disturbs myelin synthesis in fetal sheep[92]. Several studies have suggested that GCs affect the maturation of oligodendrocytes (OLs) and impair the formation of myelin[90-93]. Other studies have reported that corticosteroids enhance the expression of genes related to the synthesis of MBP and exert trophic and protective effects in the nervous system[93,94]. A study using cultured cells from rat brain has shown that dexamethasone alters oligodendroglial differentiation and myelination depending on the stage: early in the myelination process, dexamethasone has a stimulatory effect, whereas at later stages, it causes marked inhibition[95]. In addition, administration of GCs during critical periods of brain development may impair neurogenesis and myelination[86-91]. However, the precise mechanisms behind the adverse effects of GCs on myelination in the developing brain are not well understood. A recent study has shown that administration of dexamethasone during critical periods of brain development induces degenerative morphological changes in OL progenitors, suggestive of apoptosis, and subsequently resulting in hypomyelination (Fig. 1)[90]. This finding suggests that dexamethasone-induced hypomyelination may be, at least partially, due to injury to OL progenitors during specific stages in the maturation of OLs, as well as inhibition of myelin formation[90].

Conclusions

Although GCs have been widely used during the antenatal and postnatal period, many issues relating to neurodevelopment remain unclear. A body of clinical and experimental evidences suggests that exposure to exogenous GCs during critical periods of brain development may exert profound effects on subsequent brain development and the regulation of a number of neuroendocrine systems function in later adult life. Thus, based on these clinical and experimental studies, there is enough evidence to advice caution in the use of GCs in the perinatal period. And when considering postnatal GCs use, the least toxic GC should be given at the lowest effective dose for the shortest possible time. Further research is required determine the potential long-term effects and mechanisms of action of GCs on brain development.

Conflict of interest

No potential conflict of interest relevant to this article was

reported.

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