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REVIEW ARTICLE

The Developing Nervous System: A Series of Review Articles

The following is the fifth in our series of review articles on the developmental biology of the nervous system and its relation to diseases and disorders that are found in newborn infants and children. In this article Drs. Edwards and Burnham examine the effect of corticosteroids on brain development. Since steroids are frequently used to prevent or treat disease in the fetus and newborn infant, it is of utmost importance to determine whether such therapy has any effect on the developing brain.

Alvin Zipursky
Editor-in-Chief

The Impact of Corticosteroids on the Developing Animal

HEATHER E. EDWARDS AND W. MCINTYRE BURNHAM

Bloorview Epilepsy Research Program and the Department of Pharmacology, University of Toronto, Faculty of Medicine, Toronto, Ontario, Canada

ABSTRACT

Infants are subjected to both endogenous and exogenous corticosteroids in the pre- and postnatal periods. Stress to the mother before birth, or to the child postpartum, can give rise to high, chronic *endogenous* corticosteroid levels caused by activation of the hypothalamic-pituitary-adrenal (HPA) axis. Physician-administered *exogenous* corticosteroids are also used in the management of a wide spectrum of pre- and postnatal conditions. The long-term effects of corticosteroids in developing humans are not well known. Studies in animals, however, indicate that both natural stress and exogenous corticosteroids can have long-lasting and deleterious effects on the body, brain, behavior, and hypothalamic-pituitary-adrenal axis of developing infants. These data suggest that exogenous corticosteroids should be administered with caution, after careful benefit/risk analyses, and that, as far as possible, the developing brain should be protected against the effects of pre- and postnatal stress. **(*Pediatr Res* 50: 433–440, 2001)**

Abbreviations:
HPA, hypothalamic-pituitary-adrenal axis
PVN, paraventricular nucleus
CRH, corticotropin-releasing hormone
POMC, proopiomelanocortin
GR, glucocorticoid receptor
MR, mineralocorticoid receptors
GABA, gamma amino butyric acid
MHC, major histocompatibility complex
11β-HSD, 11β-hydroxysteroid dehydrogenase

Infants are subjected to both endogenous and exogenous corticosteroids in the pre- and postnatal periods. When pregnant women undergo prolonged stress, for instance, such as that caused by family discord or the death of a spouse, the unborn infant is subjected to high, chronic levels of endogenous corticosteroids (1, 2). This is a result of repeated activation of the mother's HPA axis (1). Postnatally, traumatic events in the child's life give rise to high, chronic corticosteroid levels, resulting from activation of the child's own HPA axis (3).

Exogenous glucocorticoids are also used in the management of a wide spectrum of pediatric diseases. Prenatally—and in

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Correspondence: Dr. W.M. Burnham, Department of Pharmacology, Medical Sciences Building, 1 King's College Circle, University of Toronto, Toronto, Ontario, M5S 1A8, Canada; e-mail: mac.burnham@utoronto.ca
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the early postnatal period—their primary use is in the promotion of lung maturation and, thus, the prevention of respiratory distress syndrome in preterm infants (4–6). Postnatally, corticosteroids are used for a variety of diseases, such as autoimmune hemolytic anemia (7), hypoglycemia (8), CNS trauma, meningitis, and myoclonic seizures (9–11).

The long-term effects of corticosteroids in the pre- and postnatal period in humans are not known. Studies in animals, however, indicate that both antenatal stress and repeated glucocorticoid treatment can have deleterious effects. The present review summarizes animal studies of how exogenous corticosteroids and pre- and postnatal stress affect the developing brain. The review of the literature will be preceded by a discussion of the HPA axis, and its development in early life, and will conclude with results of the limited human clinical studies.

THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

A schematic representation of the HPA axis is shown in Figure 1. The limbic system, primarily *via* the hippocampus, forms a major inhibitory input to the PVN of the hypothalamus by activating GABAergic interneurons (12). The PVN neurons release CRH and, to a lesser extent, AVP into the hypophyseal portal circulation. In the anterior pituitary, CRH and AVP synergistically stimulate the corticotroph cells of the anterior lobe to release ACTH (13). ACTH, transported in the systemic circulation, interacts with the adrenal cortex to cause steroidogenesis and elevation of plasma glucocorticoids. The primary glucocorticoid in humans and most other mammals is cortisol, but in rats and mice it is corticosterone (13).

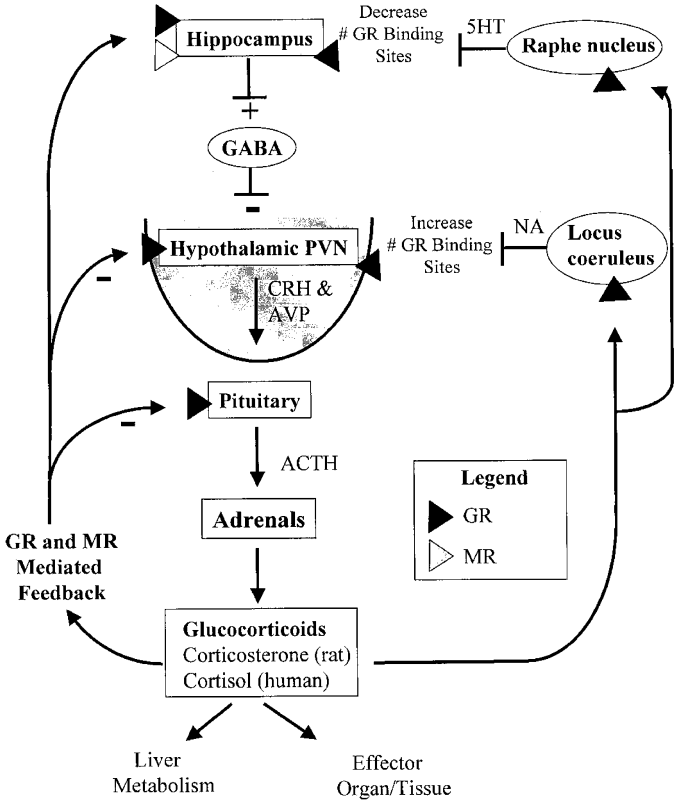

Figure 1. A schematic representation of the HPA axis and its regulation. NA, noradrenaline; 5HT, serotonin

Table 1. *Corticosteroid receptors in the brain*

Mineralocorticoid receptor	Glucocorticoid receptor
In limbic brain structures (neurons)	Widely distributed in brain (glia and neurons)
High affinity for corticosterone (Kd = 0.5 nM)	Lower affinity for corticosterone (Kd = 2.5–5 nM)
Chronically occupied (80%) by basal corticosterone	Occupied during stress
Agonist: Aldosterone (Kd = 1.5–2 nM)	Agonist: Dexamethasone, and RU 28362
Antagonist: Spironolactone	Antagonist: RU38486

Glucocorticoid feedback occurs at the level of the hippocampus, hypothalamus, and pituitary, to inhibit further HPA activity. It involves two populations of receptors: MR and GR (14) (Table 1). MR are highly concentrated in the hippocampus and septal area (15) and have a 10-fold higher affinity for circulating glucocorticoids than GR (15, 16). MR are therefore occupied (~80%) at low, basal corticosterone levels—seen in nonstress periods (16)—and are responsible for the maintenance of basal HPA activity (15). In contrast, GR are widely distributed in the brain, being most abundant in hypothalamic CRH neurons and pituitary corticotrophs (13–16). During acute stress, rising corticosterone levels cause MR to saturate and GR to become occupied (16). GR-mediated effects restore stress-induced increases in HPA activity to basal levels. They also modify neurotransmitter release from the raphe nuclei, the nucleus tractus solitarius, and the locus ceruleus (17, 18). These in turn can alter the number of GR binding sites in the hippocampus and hypothalamus (19), thereby altering feedback regulation of the HPA axis.

With prolonged stress, chronic activation of GR causes profound changes in neuronal integrity and function—resulting in altered HPA neuroendocrine regulation and behavior (20, 21). These will be discussed below.

DEVELOPMENT OF THE HPA AXIS IN EARLY LIFE

The ontogeny of MR and GR in the brain, and the development of corticosteroid feedback control, have been studied primarily in rats. As shown in Figure 2, MR (found primarily

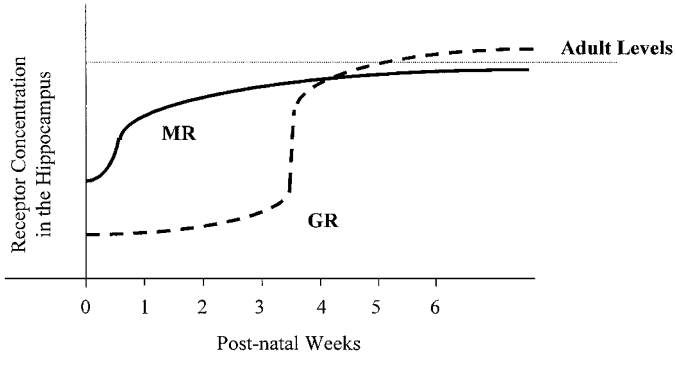

Figure 2. Developmental profile of MR and GR in the rat hippocampus. The concentration of MR is largely indistinguishable from adult levels by the end of the first week of life (26, 27). In contrast, GR are approximately 30% of adult levels at birth, and do not reach adult levels until approximately 4 wk of life (25–28). Thus, the ratio of MR/GR is much higher during the first few weeks of life in the rat.

on neurons) are largely indistinguishable from adult levels by the end of the first week of life (22, 23). High levels of MR allow the quick establishment of baseline HPA function (23). GR, on the other hand, are approximately 30% of adult values during the first few weeks of life, being found primarily on neurons (22–25). As the brain continues to develop and glial cell density increases, levels of GR in the brain increase (GR are also expressed on glia), reaching adult levels by about 30 d of life (22, 23, 25). Consistent with the slow developmental profile of GR in the brain, the ability to "rapidly turn off" a stress response does not develop fully for several weeks after birth (25, 26).

The profile of GR development in the brain lags behind that of MR; thus, there is an increased ratio of MR/GR in the rat brain during the first few postnatal weeks. The most rapid brain growth—characterized by neuronal proliferation, synaptogenesis, dendritic arborization, and increased weight (27, 28)—occurs in this early postnatal period when MR occupation predominates over GR. These neuronal events seem to be depressed by GR activation (28), which may explain the low GR levels seen at that time. Thus, dysregulation of the MR/GR balance may lead to abnormalities in the brain, behavior, and endocrine response (29–35).

EFFECTS OF ENDOGENOUS GLUCOCORTICOIDS ON DEVELOPMENT

Exposure to uncontrollable stress during pregnancy results in elevated maternal and fetal plasma corticosteroid levels (36).

How fetal corticosteroid levels rise is somewhat controversial. The first possibility is that there is a direct transfer of maternal corticosteroids across the placenta (37). Some authors, however, report that access of maternal endogenous corticosteroids to the fetus is low because of the placental expression of the enzyme 11β-HSD, which converts corticosteroids to inactive products (cortisone, 11-dehydrocorticosterone) (38). Unlike endogenous corticosteroids, 11β-HSD has a low affinity for synthetic glucocorticoids (39), and so dexamethasone and betamethasone pass rapidly from mother to fetus.

The second possibility is that maternal CRH released by the hypothalamus during times of stress may cross the placenta and activate the fetal HPA axis directly, which would explain the elevated fetal levels. Studies in rats, however, indicate that the transfer of maternal CRH across the placenta is restricted (40).

Lastly, recent studies in humans suggest that elevated maternal glucocorticoids can stimulate the production of placental CRH—which is identical to hypothalamic CRH in structure, immunoreactivity, and bioactivity (41). Placental CRH may therefore enter the fetus and activate the HPA axis (42).

Effects on the body. In the primate, guinea pig, rat, and mouse, chronic maternal stress during late gestation permanently alters fetal growth and development (27, 43–45). In rhesus monkeys, early prenatal stress reduces fetal birth weight and does so more than mid- to late prenatal stress (46). In rats, male offspring of stressed mothers, or mothers treated with exogenous CRH during late gestation, show signs of demasculinization. They have shorter anogenital distances at birth (47), and have a 20% reduction in size of the suprachiasmatic nucleus in the brain—a structure involved in neuroendocrine control of male sexual behavior in rodents (48).

Effects on the brain. Late-gestation restraint stress (4 h/day, d 15–17) in rats causes neurotoxic changes of neurons in the fetal PVN such that neural processes are shortened and apoptosis of neurons is increased (49). Prenatal stress also has been shown to have postnatal effects on neurotransmitters, including serotonin (50) and the catecholamines (51). Development of forebrain cholinergic systems is altered by prenatal stress, because hippocampal acetylcholine release in adult male and female rats is increased in response to mild stress (52).

Recent studies in our laboratory have shown that prenatal stress (*i.e.* restraint stress under bright light for 1 h, three times per day) during early or late pregnancy in the rat significantly lowers seizure threshold in the dorsal hippocampus of 14-d-old male and female offspring (Fig. 3*A* [Edwards *et al.*, submitted for publication]). We also found that prenatal stress during late, but not early, gestation also significantly facilitates the development of kindled seizures (Fig. 3*B*). These data suggest that prenatal stress increases excitability of the brain, which enhances its vulnerability to developing seizures.

Effects on behavior. Stress during pregnancy (*i.e.* immobilization, restraint, crowding, repeated electric tail shocks, or noise) in rats and primates results in offspring with sleep disturbances (53), reduced juvenile play and social interaction (54), increased frequency of mutual clinging (55), attention deficits (56), decreased exploratory behavior in a novel environment (57), and enhanced fear (54). Increased levels of fear and anxiety may relate to a decrease in amygdaloid GABAergic activity resulting from prenatal stress (58, 59). Fear and anxiety are normally inhibited by agents that facilitate GABAergic transmission (58).

Effects on neuroendocrine function. Chronic maternal stress during late gestation in the primate and rat permanently alters HPA function in the offspring (43). Offspring of prenatally stressed rhesus monkeys (unpredictable noise during mid- to late gestation [d 90–145]), for instance, have higher ACTH and cortisol levels than control offspring (60). In the rat, elevated maternal glucocorticoid levels during the third week of gestation (pregnancy = 21 d) produce a permanent 70% reduction in MR and a 30% reduction in GR in the hippocampus of prenatally stressed offspring (61). This reduction was not seen on postnatal d 3 (neonatal period), but was apparent by postnatal d 21 (weanling age) (61). Down-regulation of receptors as a result of prenatal stress must therefore occur gradually over the course of development.

These rat offspring—once born—have an altered "set point" for negative feedback, giving rise to higher basal secretion of CRH and adrenal corticosterone (31, 32). They also have enhanced sensitivity to stress-induced ACTH, giving an exaggerated stress response (31, 32, 62). Such increases in basal corticosterone levels accelerate the appearance of age-related neural and cognitive deficits in rats, including atrophy of dendritic processes and cell death (63, 64). The underlying mechanism is thought to involve energy deprivation (65), excitotoxicity (65), and disturbed calcium homeostasis (65, 66). In addition, neuronal defense mechanisms and repair by

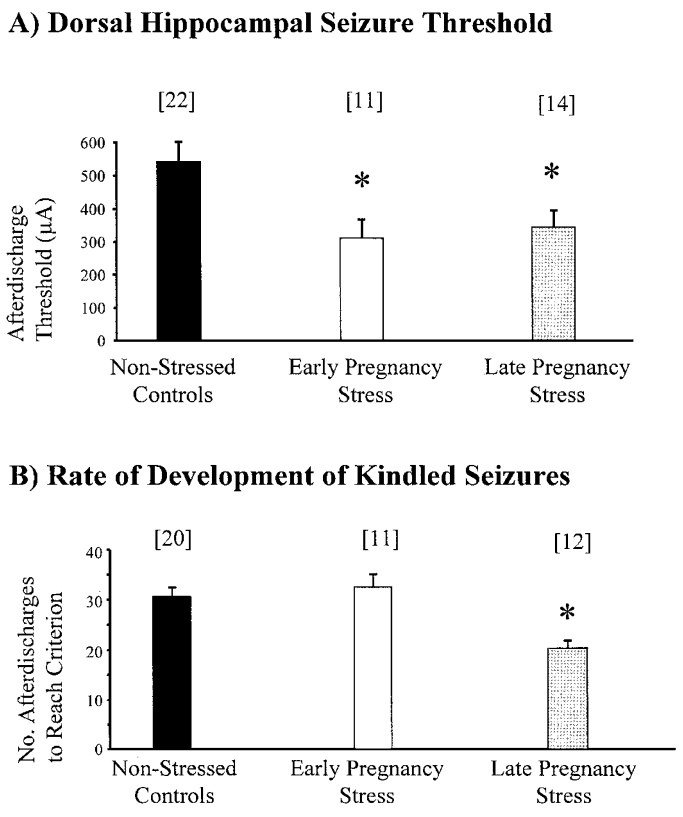

Figure 3. Rats were stereotaxically implanted with a chronic indwelling bipolar electrode in the right dorsal hippocampus on postnatal d 13. They were allowed 1 d recovery. (*A*) After-discharge thresholds were significantly lowered in postnatal d 14 offspring of mothers who were stressed during early (d 5–12) or mid- to late gestation (d 12–19). Dams were stressed *via* repeated restraint under bright light, three times per day. After-discharge threshold was defined as the minimum stimulus intensity to provoke a "spike and wave" pattern of at least 3 s on the EEG. The stimulus consisted of a 1-s train of 1 ms, 60 Hz biphasic (+ve and −ve going) square-wave pulses generated by a Grass Model S88 stimulator coupled to two Grass PSIU6 stimulus-isolation constant-current units (Grass Instruments, Quincy, MA, U.S.A.). Stimulation was begun at 20 μA and increased in steps of 20 μA until an afterdischarge was triggered. The interval between stimulations was 1 min. A Grass Model 7D polygraph was used to record electroencephalographic activity. (*B*) Kindling rates were significantly lowered in offspring of mothers who were stressed during mid-late gestation (d 12–19). Kindling involved suprathreshold stimulations (100 μA above threshold) every 15 min over a 2-d period (postnatal d 14–15). Convulsive responses, when they developed, were scored accordingly: stage 1 (mouth clonus), stage 2 (head nodding), stage 3 (forelimb clonus), stage 4 (rearing), stage 5 (loss of postural control). Stimulations were continued until three stage 5 seizures had been evoked. Data for *A* and *B* were statistically similar between male and female pups, and were thus combined. Parentheses indicate the number of animals tested in each experimental group. Asterisks indicate significant difference from control animals (Duncan's multiple range test; $p < 0.05$).

neurotrophins are impaired by corticosteroids (65). All of these changes can be prevented by blocking the mother's stress-response during pregnancy (67).

Reversal of stress effects. Although the potential consequences of prenatal stress are great, environmental events such as maternal care and handling during the postnatal period reverse the prenatal stress-induced deficits in hippocampal corticosteroid receptors and the alterations in HPA hormone secretion (43, 68). For example, fostering of prenatally stressed pups onto other dams prevents the decrease in hippocampal MR and the rise in basal glucocorticoid levels, lowers hypothalamic CRH levels, and enhances open-field exploration–an indication of decreased anxiety in animals (43, 69–71). This occurs as a result of the foster mother spending more time than the biologic mother in pup-directed activity (71). Early postnatal handling by experimenters (15 min daily for the first few weeks of life) similarly reverses the effects of prenatal stress, by altering the behavior of the mother upon the pups' return (*i.e.* increased licking and grooming of the pups) (70). Available data indicate that maternal care triggers thyroid hormone release, which appears to activate ascending serotonergic projections to the hippocampal region of the brain (72). Serotonin causes long-lasting increases in GR number in hippocampal neurons, enhancing the negative feedback sensitivity to circulating corticosteroid levels (72, 73). This promotes the rapid recovery of HPA function.

EFFECTS OF EXOGENOUS GLUCOCORTICOIDS ON DEVELOPMENT

Mammals exposed to chronic high levels of exogenous glucocorticoids during early development exhibit morphologic, physiologic, and behavioral modifications in later life. The precise nature of these is dependent on the dose of the steroid, the developmental stage at which the exposure occurs (74, 75), and the species studied (76–78). In animals that give birth to relatively mature young (sheep, guinea pigs, and primates), maximal brain growth and a large proportion of neuroendocrine maturation (including corticosteroid receptor development) takes place *in utero* (76, 77). In species that give birth to immature young (rats, rabbits, and mice), much neuroendocrine development occurs in the postnatal period (78). Thus, glucocorticoid treatment will impact on different stages of brain development depending on the species.

The discussions below will first consider the effects of prenatal and then postnatal exposure.

PRENATAL EXPOSURE

Effects on the body. In rhesus monkeys, daily administration of betamethasone (i.m.) to pregnant animals during the last trimester causes a significant reduction in brain, lung, liver, pancreas, heart, and adrenal weight in the fetus (79). Similarly, chronic administration of betamethasone (0.5 mg/kg) in sheep, or dexamethasone (0.1 mg/kg) in rats, during late gestation causes fetal growth retardation (80, 81). In mice, maternal treatment with prednisolone on d 13–18 of pregnancy causes offspring to have delayed development of eye opening, lifting, walking, and gripping (82).

Effects on the brain. Administration of even a single dose of dexamethasone to pregnant rhesus monkeys during the last trimester produces dose-dependent neuronal degeneration in the hippocampal CA1–CA3 fields of offspring (83). The degeneration is more severe with multiple injections than with single injections of the same total dose (83). In addition, when pregnant monkeys receive multiple dexamethasone treatments, their offspring (at 20 mo of age) have 30% fewer hippocampal neurons than control offspring (84).

In rats, antenatal glucocorticoids administered on d 17–19 of pregnancy have been shown to promote early maturation of the dopamine systems in the forebrain (51). As well, dexamethasone exposure (0.1 mg/kg) in the last week of gestation causes decreased serotonin turnover in the neocortex, hippocampus, hypothalamus, and midbrain in offspring at 3 and 14 wk of life (50). It also reduces norepinephrine turnover in the cerebellum and forebrain (51), and norepinephrine content in the hippocampus and neocortex (50). Concentrations of GR mRNA and MR mRNA in the hippocampus are reduced by >20% (80). These alterations in corticosteroid receptor levels would be expected to alter the feedback control of glucocorticoid secretion.

Effects on behavior. Infants of pregnant rhesus monkeys exposed to ACTH for 2 wk show impairments in motor coordination and muscle tone, have shorter attention spans, and are more irritable and difficult to console than control animals (85).

In rats, chronic treatment of pregnant dams during the last trimester with corticosterone results in sex-specific alterations in motor activity in adult offspring (86). Exploratory activity in a novel environment, for instance, is increased in adult male, but not female, offspring (86). Also, daily dexamethasone treatment (0.1 mg/kg) during the last week of gestation alters sexual behavior, such that male offspring become demasculinized and somewhat feminized (87). In mice, a single injection of dexamethasone on gestational d 14 causes differences in anxiety, memory, and socialization in the offspring (45).

Effects on neuroendocrine function. A single injection of dexamethasone (5 mg/kg) to pregnant rhesus monkeys at 132–133 d of gestation induces an irreversible degeneration of hippocampal dentate granule neurons and CA3 pyramidal neurons (84). This attenuates corticosteroid negative feedback, thereby permanently elevating basal and stress stimulated cortisol levels in the juvenile offspring (84).

In rats, dexamethasone treatment during late gestation causes pups to have permanently decreased glucocorticoid feedback and, hence, increased basal plasma corticosterone concentrations (32, 50, 80). As a consequence, the offspring of dexamethasone-treated mothers have high blood pressure (80) and suppressed immune function (88).

Thus, both rat and primate studies show that exposure to prenatal glucocorticoids leads to long-term increases in HPA tone. Increased HPA tone throughout life has a significant impact on adult health, because of the chronic exposure of tissues to glucocorticoids. In humans, elevated concentrations of cortisol are associated with atherosclerosis, heart disease, immunosuppression, diabetes, and cognitive impairment (89, 90).

Postnatal Exposure. The effects of postnatal exposure are less dramatic than the effects of prenatal exposure, but can be significant in species where large amounts of neural growth take place after birth.

Effects on the body. In the neonatal rat, a single injection of dexamethasone (0.2 or 1 mg/kg s.c. on postnatal d 7) causes an acceleration of developmental landmarks such as incisor eruption, eye opening, and motor skill, and a retardation of body growth and vaginal opening (91). It also reduces whole brain and regional weights (frontal cortex, cerebellum, and brain stem) as measured on postnatal d 28 (92). Repeated neonatal dexamethasone (1 mg/kg) treatment causes a significant increase in surfactant protein D content in the rat lungs (93). It also increases bone mineral density and bone mineral content in male, but not female, rats (94).

Effects on the brain. Administration of glucocorticoids can be neuroprotective against hypoxia-ischemia in the early postnatal period (95). This effect seems to involve a GR-mediated decrease in basal metabolic energy requirements and/or an increase in the availability or efficiency of glucose utilization (95). Also, cortisone treatment in neonates seems to prevent excessive astrocytic proliferation in response to hypoxia-ischemia by stimulating the activity of microglial cells through enhanced expression of MHC class I antigens (96).

Postnatal administration of glucocorticoids can, however, have deleterious effects on brain development (20, 97). Rates of neurogenesis, neuronal migration, and cell death reach maximal levels during the stress hyporesponsive period in the rat (postnatal d 2–14) when circulating corticosterone is low (28). Acute administration of glucocorticoids during this period causes atrophy of dendrites in various hippocampal subfields (20), permanently decreases cerebral cholesterol levels, and causes an irreversible decrease in brain weight and myelination of fibers (98). In the dentate gyrus, acute postnatal glucocorticoid treatment inhibits neurogenesis and decreases cell death (28). Thus, although the number of granule neurons appears constant, electrophysiologic studies indicate their function to be abnormal (99). Specifically, early glucocorticoid treatment alters the normal spatial extent of the perforant pathway distribution to the dentate gyrus, measured by extracellular field potential negativity of granule cell neurons (99). It also reduces the ability of entorhinal afferents to activate dentate granule cells, measured by stimulus response functions (99). Such chronic abnormalities in dentate gyrus electrophysiology might explain, at least in part, the behavioral impairments on spatial learning tests in those same animals (100).

In the rat, postnatal glucocorticoid treatment causes different populations of neurons to survive in the dentate gyrus than would normally do so (28). This may reflect an impairment of neuronal migration (101, 102), in as much as corticosteroids decrease the production of radial glia (28), and newly generated neurons preferentially migrate along radial glia (28, 102). Alterations in neural migration may predispose the infant brain to pathologic conditions, such as cortical dysplasia. Rats with cortical dysplasia, induced by intrauterine injections of methylazoxymethanol acetate, are susceptible to developing seizures (see (103) for a review). Clinically, cortical dysplasia is often found in patients with a history of medically refractory epilepsy (104). Taken together, we hypothesize that glucocorticoids may cause abnormalities in neuronal migration and cortical dysplasia, thereby altering seizure vulnerability. No clinical studies to date have tested this hypothesis, although studies in animals are currently underway in our laboratory.

Effects on behavior. Exposing the developing nervous system to hormones of the HPA axis can produce marked long-term effects on behavior. Male rat pups injected with 25 μg of ACTH on d 2–7 postpartum exhibit poor learning performance

in a shuttle box as adults, are slow to acquire reversal learning, and exhibit an exaggerated startle response (105). Rat pups treated daily with glucocorticoids during the first two postnatal weeks show delayed development of the startle reflex, of swimming ability, and of cortical evoked responses to auditory, visual, and sciatic nerve stimulation (106–108). As adults, glucocorticoid-treated animals show increased voluntary running in activity wheels and decreased motor coordination (109). They also demonstrate increased immobility in closed-field tests and enhanced defensive burying activity (110).

Effects on neuroendocrine function. A single injection of dexamethasone to 7-d-old rats results in a significant depletion of GR from the cytosol of the brain. The effect is dose-dependent, beginning with the dose of 0.04 mg/kg (s.c.), which is far lower than the clinical dose used in obstetrics (0.4–0.5 mg/kg) (92). Repeated injections of dexamethasone (on postnatal d 1, 3, and 5) in the rat similarly cause down-regulation of GR in the brain (111).

Unaltered MR expression might explain why basal levels of circulating corticosterone are not affected by postnatal glucocorticoid treatment (110, 111)—a result that contrasts sharply with the prenatal effects of exogenous glucocorticoid treatment.

IMPLICATIONS FOR HUMANS

In animals, pre- and postnatal stress, as well as exogenous administration of glucocorticoids during pregnancy, lead to long-lasting effects on the function of the HPA axis in the offspring. Although the clinical data are limited, they suggest that similar effects may occur in humans, and that they may create the substrate for later developmental, behavioral, and mood disorders.

Clinical studies on the effects of maternal prenatal stress, for instance, suggest that repeated activation of the HPA axis—and the resultant high serum levels of endogenous corticosteroids—can cause a variety of long-term sequelae in infants (43). Maternal stress during the third trimester of pregnancy is associated with adverse birth outcomes, which include preterm birth (1), fetal growth retardation (112), delays in early motor development (42), behavioral abnormalities (3, 113, 114), and sleep disturbances in the infant (43). Maternal stress has also been linked to the development of psychiatric disorders, such as schizophrenia and depression in later life (3). Abnormal HPA regulation in the unborn child, and hence glucocorticoid secretion, has been linked to the acceleration of behavioral sensitization and drug-seeking behavior, to increased emotionality, shyness and avoidance behavior, and to decreased sociability of young children (114, 115). No effect on cognitive ability was seen (114). Thus, prenatal stress in mothers has important effects on HPA function and on the later physical and mental health of the unborn child.

With regard to postnatal stress, there is evidence that links parental loss during early childhood to an increased risk for major depression and generalized anxiety disorders (2, 3, 43, 113). These children also show a permanent elevation in plasma cortisol, which may enhance their vulnerability to disease later in life (*i.e.* atherosclerosis, diabetes, etc.) (42, 89, 90, 113).

Studies on the effects of *exogenous* corticosteroids are few in number, and have been limited to the effects of prenatal administration. Randomized trials have shown no apparent neurologic or cognitive effects in children treated prenatally with a *single* course of corticosteroids (4–6). The current trend in clinical practice, however, is to increase the number of corticosteroid treatments when the risk of preterm delivery persists (10). Such repeated glucocorticoid treatment in pregnant women has been shown to reduce head circumference in children (44). It has also been associated with subtle effects on neurologic function, including reduced visual closure and visual memory, in 6-y-old children (116). Lastly, repeated dexamethasone treatment in early pregnancy—because of increased risk of congenital adrenal hyperplasia—results in children with increased emotionality, unsociability, avoidance, and behavioral problems (114).

Both endogenous and exogenous corticosteroids can have significant and deleterious effects in animals. Although there are, as yet, relatively few data on the long-term effects of corticosteroids in developing humans, the data that do exist suggest that humans show effects similar to those seen in animals. These data suggest that glucocorticoids should be administered with caution.

There are, however, circumstances in which the benefits of administering corticosteroids outweigh the risks. For example, autoimmune hemolytic anemia results from the self-destruction of red blood cells. Left untreated, the accumulation of bile pigment causes severe jaundice that subsequently leads to brain damage. As development proceeds, a pattern of cerebral palsy emerges at approximately 6 mo with uncoordinated movement, deafness, disturbed vision, and speech difficulties (117). This condition is preventable because corticosteroid administration modifies the immune response and, thus, resolves the hemolytic crisis (118). As another example, hypoglycemia—common in infancy and childhood—can cause long-term neurologic damage and mental retardation (119). Neonatal administration of exogenous corticosteroids promotes glucose homeostasis and, thus, protects the brain from hypoglycemia-induced injury (120). Lastly, ACTH and prednisone can be enormously valuable in the treatment of early childhood epilepsy, particularly infantile spasms (121, 122). If untreated, repeated seizures may cause serious brain damage (123).

In conclusion, the available literature indicates that exogenous corticosteroids should be administered only after careful consideration of the benefits and risks, and that, as far as possible, the developing brain should be protected against the effects of pre- and postnatal stress.

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