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REVIEW ARTICLE

Glucocorticosteroids Effects on Brain Development in the Preterm Infant: A Role for Microglia?

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Abstract: Prematurity, observed in 15 million births worldwide each year, is a clinical condition that is a major cause of neonatal mortality and morbidity in the short and long term. Preterm infants are at high risk of developing respiratory problems, sepsis, and other morbidities leading to neurodevelopmental impairment and neurobehavioral disorders. Perinatal glucocorticosteroids have been widely used for the prevention and treatment of adverse outcomes linked to prematurity. However, despite their short-term benefits due to their maturational properties, some clinical trials have shown an association between steroids exposure and abnormal brain development in infants born preterm. Neuroinflammation has emerged as a preeminent factor for brain injury in preterm infants, and the major role of microglia, the brain resident immune cells, has been recently highlighted. Considering the role of microglia in the modulation of brain development, the aim of this review is to summarize the effects of endogenous and exogenous glucocorticosteroids on brain development and discuss the possible role of microglia as the mediator of these effects.

Keywords: Prematurity, microglia, glucocorticosteroids, antenatal, prenatal, brain development, neuroinflammation.

1. INTRODUCTION

Prematurity, defined as a birth before the 37 weeks of gestation, affects 15 million infants every year. The etiology of preterm birth is multi-factorial, and risk factors include maternal stress, infection, fetal and/or placental anomalies [1]. This clinical condition, observed in 11% of global births, represents a leading cause of neonatal mortality and morbidity in the short and long term [1, 2]. Infants born preterm are at high risk for developing early or late-onset sepsis, respiratory problems including respiratory distress syndrome and Bronchopulmonary Dysplasia (BPD), and brain injury including Intraventricular Hemorrhage (IVH) and Periventricular Leukomalacia (PVL) [1]. Besides these short-term adverse clinical outcomes, epidemiological studies point to the association between preterm birth and abnormal neurodevelopmental outcomes, including cognitive impairment [3, 4], speech delay [5, 6], and cerebral palsy [7]. In addition, over the last decade, the concept of "preterm behavioral phenotype" [8] highlighting an association between prematurity and subsequent psychopathologies, *i.e.*, Attention-Deficit/ Hyperactivity Disorder (ADHD), Autism Spectrum Disorders (ASD), and anxiety disorders [2] has gained prominence.

Glucocorticosteroids (GCs) play a major role in the perinatal management of prematurity and are given to pregnant women at risk of preterm delivery and postnatally to infants born very preterm [9-11]. Antenatal GCs have been shown to reduce neonatal mortality and major morbidities, including respiratory distress syndrome, necrotizing enterocolitis, and IVH [12]. Postnatal GCs, whose use is much more controversial, are usually used to prevent or treat BPD [13, 14]. Besides their specific therapeutic effects, clinical studies have shown that both antenatal and postnatal GCs influence the neurodevelopment of preterm infants [15-18].

Microglia, the brain resident immune cells, induce and regulate the brain inflammatory response along with astrocytes [19]. Neuroinflammation has emerged as a key factor for the initiation and development of brain injury in preterm infants; microglial activation has been described as one of the main mediators associated with dysmaturation of the premature brain [9, 20]. Moreover, clinical data have shown an association between circulating cytokines level, microglial reactivity, and the development of ASD [21-23].

Considering the role of microglia in the modulation of brain development, the aim of this review is to summarize the effects of endogenous and exogenous GCs on brain development and discuss the possible role of microglia as the mediator of these effects.

2. METHODS

This review summarizes the clinical and preclinical data available on the developmental effects of perinatal GCs on the immature brain. A role for microglia as a mediator of

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GCs effects on brain development has been studied based on experimental evidence. A literature search was performed in August 2020 using the PubMed library in English without any restriction of year, species, and authors. The following keywords have been used: (glucocorticosteroids and fetal development, glucocorticosteroids and preterm, glucocorticosteroids and systemic inflammation, glucocorticosteroids, stress and inflammation, glucocorticsteroids and microglia). An additional manual search was performed based on the references included in the selected research papers. The review papers were used as references only for the general concepts. Papers without abstracts were not included. Only papers that met the following criteria were included: pertinence to the subject, presence of control groups, and a clear description of experimental procedures.

3. GCs IN EARLY HUMAN DEVELOPMENT AND GCs REGULATION

The release of GCs (cortisol in humans and corticosterone in rodents) is regulated by the Hypothalamic-Pituitary-Adrenal Axis (HPA). External stimuli or an internal circadian rhythm stimulate the release of Corticotropin-releasing Factor (CRF) from the hypothalamic Paraventricular Nucleus (PVN) in the portal vessel system, inducing the secretion of Adrenocorticotropic Hormone (ACTH) from the pituitary that in turn stimulates the release of GCs from the adrenal gland [24].

Endogenous GCs have a key role in the development of organs through modulation of cell differentiation and tissue maturation [25, 26]. GCs promote the production and maturation of surfactant proteins [26] and the maturation of the skin by regulating the production of fat mass [25]. In addition, cortisol contributes to the normal differentiation of the kidney and gut, allowing renal clearance and intestinal motricity, respectively [25]. The developmental effects of GCs are not limited to peripheral organs. Endogenous cortisol and corticosterone are essential for normal brain development, and they regulate neurogenesis and neuronal migration, neurotransmitter activity, synaptic plasticity, amygdala, and hippocampal brain connectivity [27-32]. In addition, GCs regulate the development of the HPA axis shaping its activity and functionality later in life and ensuring our ability to cope and respond appropriately to external stimuli [33-36].

The dynamic balance between maternal and fetal HPA axis activity during gestation ensures that fetal development is closely dependent on maternal hormonal regulation, including GCs [9]. The first trimester of pregnancy is characterized by a predominant contribution of maternal cortisol that easily reaches the fetus through the placental circulation [37]. The placenta represents the only common site between the mother and the fetus, and its role in the modulation of fetal HPA axis activity is dependent on the expression of CRF and the enzyme 11β-HSD-2, which converts cortisol to the inactive metabolite, cortisone [26]. The expression of 11β-HSD-2 increases during gestation and serves to protect the fetus from overexposure to maternal GCs [38]. Placental CRF secretion also increases exponentially during gestation [39], reaching, by the end of pregnancy, levels comparable to those observed in response to acute psychological stress [40]. The increase in maternal CRF blood level results in an increase in cortisol secretion that, through a positive feedback loop, results in a further increase in placental CRH and cortisol levels [37, 39, 41]. The fetal HPA axis maturation starts gradually with the production of ACTH and CRH detectable respectively in the hypothalamus and in the pituitary gland early in the second trimester [37]. An increase in fetal cortisol production is observed from 23-24 weeks of gestation, with a significant rise seen only after the 30th week of gestation [37, 42, 43].

Considering the existence of this fine regulation of the fetal exposure to GCs and their important role in development, any disturbance in this balance, in particular exposure to excessive circulating GCs or preterm delivery, may result in severe changes in developmental trajectories.

4. ENDOGENOUS GCs AND BRAIN DEVELOPMENT FROM ANIMAL MODELS TO HUMAN NEONATE

The neonatal period represents a crucial period for brain plasticity, building neuronal circuitries that define subsequent behaviors and phenotypes. Hence, understanding how early experience, including stressful events and exposure to GCs, can modify these trajectories is key to deciphering the origins of neurobehavioral alterations.

The effect of early exposure to GCs has been widely studied in animal models by inducing the activation of the HPA axis in pregnant dams. This Prenatal Stress (PS) protocol results in the release of maternal GCs that reach the fetus *via* placental circulation [44]. Indeed, gestational stress has been shown to decrease the placental expression of 11β-HSD-2, the GCs inactivating enzyme, with an increase in maternal GCs levels crossing the placenta as a consequence [45]. PS was shown to induce placental and fetal brain inflammation [46] and to confer pro-inflammatory consequences on the immune system in adult rats, as evidenced by the increase of circulating peripheral blood mononuclear cells [47]. Offsprings exposed to PS show a hyper-activation of the HPA axis [48, 49] associated with an increase in anxiety behavior, a reduction of social behavior, and poor learning and cognitive performances later in life [50-53]. Moreover, these behavioral alterations are associated with a reduction in hippocampal volume, in hippocampal and dentate gyrus neurogenesis [54, 55], and in the synaptic density of the prefrontal cortex [50]. The molecular mechanisms underlying these stress-induced effects have been widely investigated, and recent studies have highlighted a role in epigenetic modifications. An increase in methylation of synaptic-related genes in the prefrontal cortex and of a GCs-induced leucine zipper gene in the amygdala has been reported in mice exposed to PS and associated with anxiety behavior and Post-Traumatic Stress Disorder (PTSD)-like symptoms in adult offsprings, respectively [50, 56].

In humans, the knowledge about the epigenetic modifications induced by the PS associated with prenatal substance exposure, psychosocial stressors, or prenatal inflammation is limited to studies on peripheral tissue as cord blood, placenta, and cord tissue collected at birth. They have revealed an association between PS and methylation HPA axis-related genes (FKBP5, NR3C1, and 11β-HSD-2) [57-60]. In contrast, the use of the MRI technique has allowed one to describe the structural alterations in the brain of infants ex-

posed to PS. Devis *et al.* recently demonstrated that infants exposed to maternal stress showed a lower cortical thickness at 7 years of age associated with subsequent depressive symptoms at 12 years of age [61]. Similarly, a retrospective study showed a reduced gray matter volume in regions associated with major depression in young adolescents exposed to maternal stress during the first 20 weeks of gestation [62]. Recently, an association between maternal cortisol level during pregnancy, amygdala connectivity, and internalizing behavior has been reported in children at 2 years of age. In particular, females exposed to elevated cortisol levels showed higher amygdala connectivity associated with evidence of internalizing symptoms [30]. In addition, higher cortisol levels in pregnant women were associated with lower IQ in children at 7 years of age [63], lower mental and psychomotor development in 3-month-old infants [64, 65], and an increase in plasma cortisol levels 24 h after birth in response to the painful procedure [66].

Maternal stress during gestation is a well-known risk factor for low birth weight and for premature birth [67-69], and data showed that maternal plasma levels of ACTH, CRH, and cortisol are biological predictors of preterm delivery in women with preterm labor [70, 71]. The consequences of preterm birth on brain development have been defined as encephalopathy of prematurity, a complex combination of white matter injury (WMI) and gray matter alterations [20, 72]. Preterm infants showed abnormal cortical folding with lower gyrification index [73] and reduction of cortical, thalamus [74], and hippocampi volumes at 2 years of age [75]. Similarly, Zhang *et al.* described a reduction in total cortical grey matter volume, white matter volume, gyrification index, and cortical surface area at 7 years of age in infants born very preterm [75, 76]. In addition, several studies have shown the presence of structural and functional alterations of brain connectivity in brain networks associated with cognition [77-79], motor abilities [80-83], language [79, 84, 85], and social and emotional behavior [32, 86, 87]. Epidemiological data showed that preterm infants are at a higher risk of developing various disorders, including ADHD, ASD, and anxiety disorders [2, 88]. Interestingly two recent studies provided evidence that preterm births resulted in alterations in connectivity involving the amygdala and were associated with impaired social ability at 2 and 20 years of age [86, 87].

While several lines of evidence clearly show the consequences of prematurity on brain development, very little information is available on the effects of PS on the immature brain. Using diffusion MRI, an association between prenatal maternal stress and development of fronto-limbic structure in preterm neonates has been reported [89]. In particular, an alteration of the uncinated fasciculus microstructure, a white matter tract that connects the limbic area in the temporal lobe with the prefrontal cortex, has been reported in preterm neonates exposed to PS and assessed at term equivalent age. In utero exposure to cortisol during gestation and the perinatal period has been discussed as one of the possible factors [89].

In conclusion, exposure to endogenous GCs during gestation can dramatically change brain structures with short- and long-term consequences on neuro-behavioral development.

5. PERINATAL EXPOSURE TO SYNTHETIC GLUCOCORTICOIDS (GCs) IN NEONATES BORN PRETERM

The recommendation of the National Institutes of Health (NIH) published in 1994 and approved by other health organizations such as the World Health Organization (WHO) and the American Academy of Pediatrics established that antenatal GCs should be administered to all women at risk of preterm labor between 24 and 34 weeks' gestation [90]. Dexamethasone and betamethasone are the two synthetic GCs used in antenatal GCs therapy because they easily cross the placenta barrier [91]. Usually, antenatal GCs should be administrated in a single course as repeated weekly courses may induce adverse events without substantial benefits [92].

After birth, dexamethasone, betamethasone, and hydrocortisone are the main synthetic GCs administrated systemically to preterm infants [93]. The guidelines of the European Association of Perinatal Medicine and of the American Academy of Pediatrics stated that the postnatal use of systemic GCs should be limited to Randomized Control Trials (RCT) [94, 95]. Moreover, the recent update of the American Academy of Pediatrics discouraged the use of a high dose of dexamethasone and highlighted the necessity for further studies to evaluate the effects of low doses [93]. Below, evidence regarding the effect of antenatal and postnatal GCs on brain development will be summarized.

5.1. Antenatal GCs

The antenatal administration of synthetics GCs remains unanimously as one of the most dramatic advances to prevent complications related to prematurity in the last 50 years. To date, more than 85% of women at risk for very preterm delivery are treated with antenatal GCs worldwide [96, 97]. They considerably reduce the incidence of respiratory distress syndrome and other major complications of preterm delivery, including IVH and necrotizing enterocolitis, and globally decrease neonatal mortality by 50% [12, 98].

Although the results of many clinical trials confirmed the beneficial effects of antenatal GCs on the short-term adverse outcomes of preterm delivery, these benefits have progressively been shown to be offset by potential long-term risks. First on fetal growth, shown by multispecies animal studies using a repetitive administration of betamethasone [99-102] that was subsequently confirmed in several clinical trials comparing single doses to multiple doses of corticosteroids in humans [103-107]. Fetus exposed to multiple courses of GCs showed a decrease in body weight, body length, and a dose-dependent reduction in head circumference [108-110] [103-105, 107, 111].

In addition to the effects on fetal growth, animal studies have simultaneously revealed the impact of this treatment on the programming of several fetal tissues and organs, including the developing brain [112-114]. These effects are observed across species and are linked to modifications of important endocrine and physiological processes. Antenatal GCs exposure was associated with high blood pressure in sheep [115] and marmoset [116], a deficit in the HPA axis in sheep [117, 118], rat [119], guinea pig [120], and in non-human primates [116, 121], and abnormalities in carbohydrate metabolism in sheep [122], rat [123] and marmoset [123].

Interestingly, two recent studies performed in sheep showed that the changes in glucose metabolism and the HPA axis induced by exposure to antenatal GCs at dosage and period of time equivalent to those used in pregnant women are observed across generations [124, 125], raising concerns about the long-term effects of this treatment in humans. However, so far, a follow-up study of children born after a single course of antenatal GCs for the prevention of respiratory distress syndrome has only revealed a possible early insulin resistance at the age of 30 without clinical effect on cardiovascular risk factors [126]. In addition, follow-up studies at 5 and 6-8 years, carried out from other randomized trials, comparing single cures to multiple cures of betamethasone did not show any differences in insulin sensitivity and blood pressure [127].

Delayed myelination of the central nervous system has been reported, at a dose similar to the dose used in human clinical trials, in sheep [128, 129] and macaque [130] after multiple courses of dexamethasone whereas reduced neuronal proliferation and an alteration of the neuronal cytoskeleton and of the presynaptic structure have been observed even after a single course in rats and baboons, respectively [128, 131]. Likewise, an effect of multiple administration of GCs on the brain surface and a reduced whole cortex convolution index, a measure of the complexity of cortical folding, have been reported in infants born at near or full-term [132]. The consequences of prenatal GCs exposure on neurodevelopment have been further highlighted by Davis *et al.* Indeed, a greater cortical thinning in the rostral anterior cingulate cortex has been associated with a higher incidence of affective disorders in the children exposed to antenatal GCs at 6 and 10 years [133]. These data are consistent with a very recent cohort study showing that exposure to antenatal GCs, compared to non-exposure, was significantly associated with mental and behavioral disorders in children, in particular in full-term children [134]. In addition, an increased rate of cerebral palsy has been observed in children born after 34 weeks gestation and exposed to 4 or more courses of corticosteroids [135], reinforcing the idea of a possible dose-dependent effect of antenatal GCs on the fetal brain.

We reported in the previous section that prenatal stress and endogenous cortisol are able to modify the genome via epigenetic mechanisms. In agreement with this result, preclinical studies provide evidence that fetal exposure to prenatal GCs is associated with developing epigenome modifications. Fetal exposure to betamethasone modified the epigenome profile in the hippocampus of guinea pigs affecting DNA methylation and histone h3 lysine 9 (H3K9) acetylation status at 24h and 14 days after birth [112, 136].

5.2. Postnatal GCs

Postnatal GCs exposure to treat or prevent the risk of BPD in the most immature babies became a very common clinical practice in the 1990s. Epidemiological data showed that in the United States, 19 to 28% of premature babies were treated with GCs [137, 138] in 1995-96, and 67% of European neonatal centers used postnatal GCs to treat BPD in 1999 [139].

Several studies showed that dexamethasone, one of the main GCs used in newborns, provides acute benefits, improving lung function, shortening the weaning time from mechanical ventilation, and reducing the occurrence and severity of BPD [140-143]. However, besides these benefits, dexamethasone exposure has been associated with gastrointestinal hemorrhage, hyperglycemia, and hypertension and in the long term with delayed growth and weight gain, all factors that reduce the benefit/risk ratio and that could interfere with brain maturation and likely account for abnormal neurocognitive development [144-148]. In contrast, hydrocortisone, given early after birth in extremely preterm infants, was not associated with adverse neurological outcomes at two years of age, despite some adverse events in common with dexamethasone, including hyperglycemia and gastrointestinal perforation [16, 149]. However, these observations were reported from a limited sample size so far and should be further confirmed, notably in long-term assessment.

Brain imaging demonstrated that postnatal GCs induce a decrease in brain growth, affecting both the cortex and the basal ganglia [150]. In addition, a follow-up of a cohort of children treated early for 4 weeks with dexamethasone showed a reduction in size and head circumference, a limitation in motor performance, and in the development quotient at school age [151]. Similarly, another follow-up study reported an increase in the incidence of cerebral palsy in infants exposed to dexamethasone [152], supporting the premise that postnatal GCs can increase the risk of impaired cognitive development in preterm infants [153, 154].

Preterm birth has been recognized as a risk factor for the subsequent development of Autism Spectrum Disorder (ASD) [155, 156]. Interestingly, several studies have reported a positive association between postnatal GCs exposure and ASD in preterm infants [15, 157, 158].

GCs can also potentiate white matter vulnerability, a major component of subsequent disability in premature babies, especially when associated with Hypoxia-Ischemia (HI), hypoglycemia, and the accumulation of glutamate leading to excitotoxicity cascade [159]. Exposure to corticosterone exacerbates the hypoxia-hypoglycemia-induced injury in hippocampal and astrocytes rats culture [160]. In agreement with the *in vitro* observations, studies performed in P7 rats, a developmental stage in which the rat brain maturation is equivalent to the moderate preterm infants [161], show that dexamethasone administration increases the HI-induced mortality and the ischemic brain injury in a dose and time-dependent way [162-164]. A recent study of Chia-Yu further evinced the role of GCs in the potentiation of white matter injury. A 3 day postnatal (P1 to P3) exposure to dexamethasone exacerbates the myelin alterations (reduction of myelin thickness and of axon caliber) induced by HI [165].

While an association between postnatal GCs and abnormal brain development has been reported in several clinical trials enrolling preterm infants, very little is known about the causal mechanism.

Dexamethasone, administrated to mice pups using a regimen that closely mimics the protocol used in neonatal intensive care units, increased brain apoptosis and biased neuronal differentiation towards an increased number of GABAergic

neurons in the cortex [166]. More recently, Kim et al. demonstrated that dexamethasone injection from postnatal day 1 to 5 induced increased apoptosis of oligodendrocytes precursor O_4 positive cells and led to defective myelination in rats [167].

Finally, Heine and Rowitch demonstrated that GCs inhibit neuronal progenitor proliferation in mice via the modulation of Sonic Hedgehog (Shh), a signaling pathway that finely regulates key processes, including cell proliferation and fate specification in the developing brain [168, 169]. More specifically, Shh has been identified as an antagonist of GCs inducing the expression of the enzyme 11β-HSD2 known to be responsible for the inactivation of endogenous betamethasone and hydrocortisone but not dexamethasone [169].

6. GCs, MICROGLIA, AND OTHER MAJOR PLAYERS INVOLVED IN BRAIN DEVELOPMENT

External and internal noxious events, including GCs exposure, elicit the activation or regulation of an inflammatory response. This physiological process is fundamental for restoring the homeostasis of the organism, and modulation of neuroinflammation is orchestrated by microglia via crosstalk with astrocytes [19].

Microglia derived from primitive macrophages originating from the yolk sack that migrate and colonize the brain during development represent 10-15% of glial cells [170]. Two migration phases have been identified: during the first 2/3 of a human pregnancy/the embryonic days 10 and 19 in rodents and the early post-natal days [171]. Microglial cells have a unique transcriptomic footprint defined by Hickman et al. as "sensome" encoding for proteins sensing endogenous and exogenous ligands [172]. Under physiological conditions, microglia constantly monitor the brain environment, undergoing morphological and maturational changes allowing them to migrate into the injury site in case of brain damage [172].

Normal brain development requires an accurate regulation of microglia activities. Indeed, studies demonstrated that microglia promote neuronal survival by releasing trophic factors (*e.g.,* Insulin Growth Factor 1 and Brain-Derived Neurotrophic Factor) [173, 174], regulate the spontaneous apoptosis of neuronal precursors, and actively contribute to their phagocytosis [175, 176], and modulate synaptogenesis by an active role in synaptic pruning [177, 178]. Besides their effects on neurogenesis and synaptogenesis, several studies show the existence of a crosstalk between microglia and oligodendrocytes progenitors (OPCs) [171]. Myelin production is defined by an initial migration and proliferation of OPCs followed by their differentiation first into pre-oligodendrocytes and then into mature oligodendrocytes [179]. Brain colonization by microglial cells occur at the time of oligodendrocytes differentiation [171] and oligodendrogenesis overlap with the period of migration of amoeboid microglia from the ventricular zone into the developing white matter [180, 181]. Moreover, studies have shown that microglia conditioned media promotes the proliferation/differentiation of OPCs subjected to growth factor deprivation and rescues their survival *in vitro* [182, 183]. Interestingly, a new microglia subset CD11c+, highly expressed during the first postnatal days, has been recently identified by Wlodarczyk *et al*. in mice [184]. This unique population was mainly observed in the developing brain between postnatal days 3 and 5 in rats and mice and is thought to contribute to myelination by releasing high amounts of the myelinogenic factor Insulin Growth Factor 1 [184].

Deregulation of microglial activities and a shift from a neuroprotective to a neurotoxic phenotype can dramatically affect the development of the brain and promote the resurgence of neurobehavioral diseases. Increasing evidence supports abnormal microglia activation being associated with the arrest of white matter maturation and neurodevelopmental disorders [185-188]. Accordingly, postmortem studies have shown diffuse microglial activation within the developing white matter in preterm infants with diffuse white matter injury [189, 190]. Moreover, an increase in microglial reactivity has been observed postmortem in the cortex, white matter, and cerebellum in infants with a diagnosis of ASD [21], for which neuroinflammation has been identified as an important risk factor [21-23].

We reported above that microglia express multiple receptors that allow them to respond to different stimuli. Both endogenous and synthetic GCs can easily cross the blood-brain barrier and reach microglial cells.

In general, microglia express the two GCs receptor subtypes: mineralocorticoid (MR) and GCs Receptor (GR) [191, 192] (Fig. **1**). In rats and mice, GR and MR are present on microglial cells at least from birth (unpublished observation). Acute GCs exposure reduced the secretion of pro-inflammatory cytokines in response to LPS and to *Staphylococcus aureus* in pure microglia cell culture [193, 194] and suppressed the NF-kB activation in response to LPS exposure *in vivo* [195]. Studies on murine BV2 microglia suggest that MR and GR differentially regulate microglia activation. Indeed, MR was shown to induce upregulation of IL-6 and TNF-α gene expression as well as NF-κB pathway activation at low/moderate GCs concentrations. This pro-inflammatory effect is suppressed by the GR-dependent pathway at high GCs concentrations [196]. A selective effect of GR receptor on microglia proliferation [191, 197] and on corticosterone-induced cell death [197] has been evidenced in BV2 microglia cells in response to treatment with Mifepristone (RU486, antagonist of GR receptor) [197]. In addition, the study performed by Vyas and collaborators using microglia/macrophage GR KO mice showed an increased amoeboid microglia cell density in the cortex, septum, and striatum in response to LPS injection [198].

The pharmacological action of GCs is finely modulated by the dose and by the exposure duration, as immediate and delayed effects could be opposed. Indeed, protracted and high levels of endogenous GCs observed in response to chronic stress or exposure to a high dose of synthetic GCs were found associated with delayed pro-inflammatory effects [199-201]. Chronic dexamethasone exposure induced a dysfunctional ramified microglia phenotype *in vitro* [202, 203]. Similarly, hippocampal ramified microglia were observed in 3-month-old mice treated for 7 days with GCs [203], and exposure to prenatal stress between the embryonic days 10 and 20 reduced the number of immature microglia in the corpus callosum and increased the number of ramified microglia [204]. In addition, maternal separation, a constant

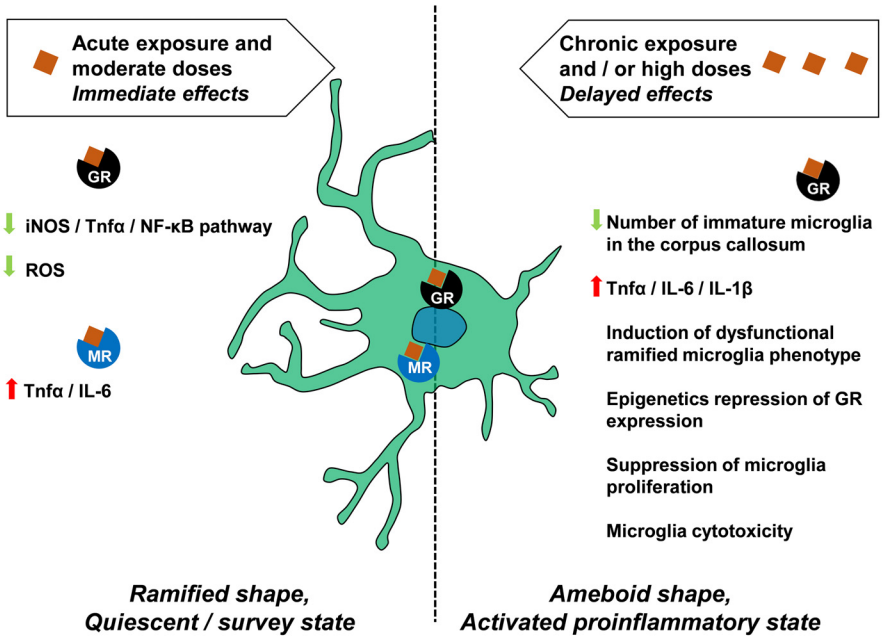

Fig. (1). Effects of glucocorticosteroids on microglia functions. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

condition in humans after preterm delivery or neonatal intensive care, is associated with an increase in microglia activation in the rat hippocampus at 15 days [205]. The underlining mechanism responsible for this abnormal microglia phenotype remains unclear, but evidence suggests that these effects may be related to epigenetic regulation of nuclear GR. Indeed, an increase of GR methylation has been observed in leukocytes and mononuclear cord blood cells in adults and infants exposed to stress early in life [206, 207], and we can hypothesize that a similar phenomenon occurs in microglia [208].

Microglia are exposed to a vast number of diffusible molecules released in the brain *via* local secretion or through blood circulation. Hence, we can hypothesize that the effect of GCs on microglial functions is also mediated by an indirect effect on GCs microglia signaling. Our group recently demonstrated a key role of the neuropeptide oxytocin in the modulation of microglial reactivity in a rat model of fetal growth restriction. Using a multispecies approach, we demonstrated that carbetocin, an analog of oxytocin, was able to reduce perinatal brain injury by targeting microglia [188]. Interestingly, the oxytocin system and the HPA axis are reciprocally connected. Exposure to stress or a high dose of GCs stimulates the release of oxytocin, whereas oxytocin reduces the GCs secretion preventing brain exposure to excessive levels of GCs [208]. An abnormal release of oxytocin or downregulation of oxytocin receptor may be related to pro-inflammatory microglia shift induced by high levels of GCs.

Finally, in the adult brain, GCs exposure is able to potentiate synaptic glutamate release [209]. Hence, they could modulate the complex homeostasis of the synaptic glutamate system, including notably regulation of glutamate receptors. This emerging function of GCs remains to be confirmed in the developing brain and may contribute to the long-lasting neurobehavioral effects of early life brain GCs exposure. Both ionotropic and metabotropic glutamate receptors are expressed in microglia, and these receptors were found to regulate microglial functions. In particular, type 4 [210] and type 5 metabotropic glutamate receptors [211], when activated, are able to reduce microglial activation. In addition, we recently demonstrated that type 3 metabotropic glutamate receptors play a central role in the regulation of microglial reactivity in the immature brain and that their selective pharmacological activation mitigates the pro-inflammatory phenotype associated with fetal growth restriction [212].

7. PERINATAL INFLAMMATION AND THE DEVELOPING BRAIN

The preclinical and clinical data reported in the previous sections clearly evidenced the effects of GCs/stress exposure on brain development and the potential ability of GCs to modulate microglia activation. On the other hand, several studies highlighted the role of inflammation on the occurrence of prematurity and on the effect of prematurity on brain development. Perinatal inflammation is indeed a major risk factor for prematurity and the best predictor of poor neurological outcome, leading to permanent sequelae in 9 million infants every year [213-215]. Conversely, prematurity and fetal growth restriction are associated with postnatal systemic and central inflammation both in humans and in preclinical models [185, 216-220]. Adverse perinatal events associated with systemic inflammation are known to activate microglia [221], deregulate the microglia signaling pathway [222], and sensitize the developing brain to a secondary hypoxic or excitatory insult [223], leading to diffuse white- and grey-matter damage [224]. Abnormalities in axonal growth and synaptic pruning [225] and blockade of the oligodendroglial

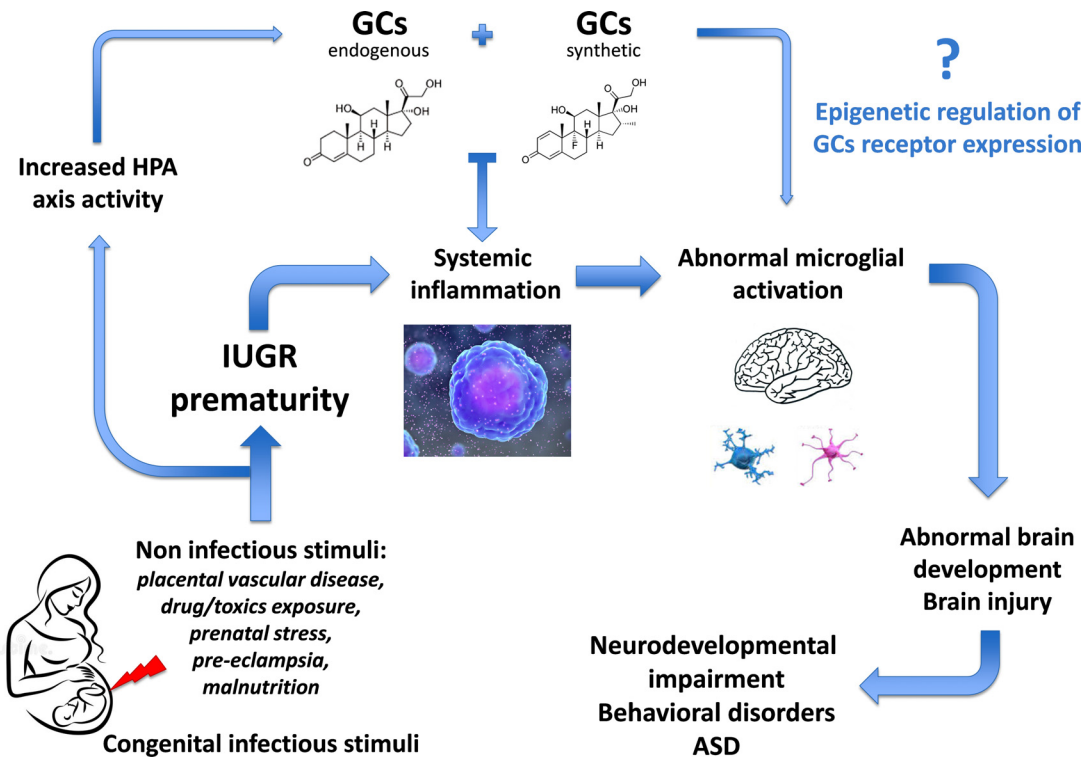

Fig. (2). The reduction of systemic inflammation as a possible mechanism of Glucocorticosteroids (GCs) effects on brain development in infants born preterm or growth restricted (IUGR). *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

lineage leading to defective myelination [226] are the major cellular processes involved in these developmental vulnerabilities that are also associated with microglial activation.

The link between GCs exposure, microglia activation, and neurodevelopmental disorders in premature or fetal growth-restricted infants has not been investigated yet. However, the ability of microglia to respond to GCs and their important role in brain development support the hypothesis of a causal relationship between stress/GCs-induced abnormal microglia response and modulation of brain development.

Perturbation of microglia functions early during the development is associated with long-term anatomical and behavioral alterations, and GCs and stress can have an important role in this context [227-230]. In addition, early stress can influence microglia susceptibility to secondary adverse events contributing to the insurgence of brain pathological alteration later in life [231]. Based on the multiple-hit hypothesis of perinatal brain injury [232], we could hypothesize that the inflammation observed in the preterm represents a predisposing factor for the insurgence of adult brain disease. Primed microglia can thus respond to adverse postnatal events such as GCs exposure and stress and potentiate the stress-induced brain damage. Chronic stress was reported as an inductor factor in the insurgence of brain anomalies identified in animal models of depression-like behavior [233-235], Parkinson's [236], and Alzheimer's disease [237-239], and effects of glucocorticoid on microglia cells reactivity are interestingly highlighted as the basis of these phenotypes. Synaptic alteration and neuronal atrophy observed in the prefrontal cortex of mice exposed to chronic unpredictable stress were indeed recently associated with an abnormal microglia activation, modulated by the treatment with RU486, a pharmacological antagonist of GCs receptor [233, 234]. Similarly, loss of dopaminergic neurons in the substantia nigra and inflammatory response to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration were increased in GR microglia/macrophage KO mice [236, 240].

8. GCs AND THEIR ACTION ON SYSTEMIC INFLAMMATION IN PRETERM INFANTS

In addition to their central effect on microglia, GCs have potent peripheral activity on systemic inflammation. The fetal systemic inflammatory response syndrome, originally defined as an elevation of the fetal plasma IL-6 concentration [241], is a clinical condition defined by systemic activation of the immune system [242] that predisposes the fetus to further brain injury or prevents repair and regeneration, and therefore is identified as an important risk factor for neurodevelopmental disorders [241, 243, 244]. Studies performed both in animal models and in humans demonstrated an association between systemic inflammation and abnormal brain development. A hypoxic-ischemic injury was found associated with the activation of microglia/macrophages, astroglia, and CD4 lymphocytes in the rats' brain even 35 days after injury [245] and to the activation of T-lymphocytes 3 months after HI in mice [246]. Similarly, increased levels of blood inflammation-related proteins in 7 and 14 days infants were associated with impaired mental and motor development at 2 years of age [247], and higher TNFα plasma levels were ob-

served in children with cerebral palsy at school age [248]. This has led to the recent development of the concept that non-infectious inflammatory stimuli may contribute to perinatal brain damage as a secondary and tertiary phase insult [249, 250].

In this context, synthetic GCs might act through their inhibitory actions on pro-inflammatory mediators and protect the developing brain from exposure to an "Intermittent or Sustained Systemic Inflammation" (ISSI) [249] (Fig. **2**). GCs are well known for their systemic anti-inflammatory action, and this property promoted their use for the treatment of pro-inflammatory morbidities associated with prematurity [251]. Some studies suggest a link between postnatal GCs and the regulation of biological markers of inflammation. Dexamethasone treatment in preterm infants at risk for chronic lung disease was found to reduce the number of neutrophils in the lung aspirate fluid and decrease the concentrations of leukotriene, another pro-inflammatory mediator, when given 10 days after birth [252]. However, a causal link between the short-term benefits of postnatal steroids in the treatment of BPD and a reduction in the systemic inflammatory response syndrome frequently observed in preterm infants remains to be determined. Regarding antenatal GCs, a very limited number of studies investigating cord blood samples are available with discrepant conclusions. Antenatal GCs did not appear to change the concentration of plasma inflammatory-related protein in infants born before 28 weeks of gestational age [253]. Similarly, no difference in the cord plasma level of IL-6 and IL-8 have been observed in infants exposed to antenatal GCs before 34 weeks of gestational age. In contrast, an increase in IL-6 cord plasma levels has been observed in exposed preterm infants before 32 weeks of gestational age, whereas lower blood levels of IL-6 and reactive oxygen species have been reported in very low birth weight preterm infants. The potential anti-inflammatory properties of perinatal GCs treatment could be viewed in balance with negative systemic outcomes. However, the reduction in perinatal inflammation was observed in the short term and without giving particular attention to microglia function. Medium (middle) and long-term specific effects of perinatal GCs treatment on microglia function and programming in the developing brain should be studied in more detail.

CONCLUSION

Antenatal and post-natal GCs represent very common clinical practices currently used to prevent or treat complications associated with premature birth. A vast literature in recent years has demonstrated an important role for neuroinflammation and microglia functions in the vulnerability of the developing brain in the development of brain lesions and brain plasticity in preterm infants. Recent studies related to the effect of GCs on brain development strongly suggest potential interactions between GCs exposure and the modulation of microglia functions. These effects could be directly mediated by the activation of GCs receptors in microglia or by modified crosstalk between the oxytocin system and the HPA axis. Regulation of microglial functions and phenotypes by GCs and, in general, hormonal environment during the perinatal period appears to be crucial in preventing neurodevelopmental handicaps associated with prematurity and fetal growth restriction.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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