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Standard Review

Mechanistic links between maternal bacterial infection and cerebral palsy

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Maternal bacterial infection is known as a causal factor for preterm labor and neonatal morbidity. In recent years, both epidemiological and experimental studies have identified maternal bacterial infection as one of the causal factors for the development of cerebral palsy (CP) in the offspring. This review examines accumulating evidence that as critical mediators of the host's response to fighting the infecting bacteria, inflammatory cytokines and oxidative stress also play important roles in maternal bacterial infection-induced white matter damage and ultimately the development of CP in the offspring. Understanding the actions of cytokines and oxidative stress in CP development could potentially lead to novel and effective therapeutic strategies.

Key words: maternal infection; cerebral palsy; lipopolysaccharide; cytokine; oxidative stress

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INTRODUCTION

Cerebral palsy (CP) is defined as a group of non progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development (Mutch et al., 1992). Cerebral palsy is usually clinically defined at 4 - 5 years of age (Neufeld et al., 2005), and it is the most common childhood disability in neuromotor development, affecting as many as every 2 - 3 out of 1000 children in the U.S. each year (Schendel et al., 2002). The signs include motor deficits (Rosenbaum et al., 2007). CP patients may also exhibit psychoemotional retardation, seizure, mental retardation, speech delay, perceptual and sensory deficits, and many other problems (Rahman et al., 2004; Rosenbaum et al., 2007; Singhi et al., 2003). The most prevalent pathological lesion seen in CP subjects is white matter damage, varying from periventricular leukomalacia (PVL) to diffuse non cystic myelination disturbances within the white matter, characterized by hypomyelination and loss of oligodendrocytes (OLGs), the myelin-forming cells of the central nervous system (Back et al., 1998; Johnston and Hoon, 2006). Both prenatal and postnatal factors have been found to contribute to the development of CP in infants (Jacobsson and Hagberg, 2004), and maternal bacterial infection is one of the prenatal factors that have been found to be associated with fetal brain damage and increase the risk of developing various neurological disorders including CP in the offspring (Babulas et al., 2006; Neufeld et al., 2005).

Bacterial infection has been found to increase the levels of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 in the peripheral system and in the brain of rodents (Koedel et al., 2004; Stoycheva and Murdjeva, 2005; Turrin et al.,

2001). In the meantime, bacterial infection has also been found to increases the formation of reactive oxygen species (ROS), such as oxygen ions, free radicals, and peroxides, in the liver, heart, lung, blood, and brain in experimental animal models, leading to oxidative stress (Sakaguchi and Furusawa, 2006; Victor et al., 2005). The inflammatory cytokines and ROS act as critical mediators of the host's immune response to fight infecting bacteria (Knight, 2000; Sikora, 2000; Slifka and Whitton, 2000). There is also accumulating evidence that the inflammatory cytokines and ROS may also mediate the development of CP. Several reviews focused on the incidence and prevalence, classification, diagnosis, and prognosis of CP have been published recently (Green and Hurvitz, 2007; Jones et al., 2007b). The objective of this review is to examine the relationship between maternal bacterial infection and the development of CP in the offspring, and the role of inflammatory cytokines and oxidative stress in the induction of white matter damage in the offspring following maternal bacterial infection.

Maternal bacterial infection as a causal factor for CP

There is accumulating evidence that maternal infection not only contributes to pre-term labor, but also increases the risk for neurological pathologies in the offspring (Romero et al., 2007). Several population-based case control studies have found that maternal infection is correlated with the occurrence of CP in preterm and term infants (Matsuda et al., 2000; Neufeld et al., 2005). Furthermore, Wu et al., (2000) conducted a meta-analysis on studies examining the association between CP and clinical chorioamnionitis, an infection of the mem-branes (chorion and amnion) and amniotic fluid, and found that clinical chorioamnionitis is strongly associated with the development of PVL and CP in both preterm and term infants (Wu and Colford, 2000). These studies suggest that maternal infection is a significant risk factor for the development of CP in infants.

Animal model systems using prenatal administration of live bacteria or bacterial products to mimic maternal bacterial infection have been employed to directly examine the linkage between maternal bacterial infection and white matter damage in the offspring (for details, see Table 1). Intracervical administration of 100 µg/kg lipopolysaccharide (LPS, endotoxin), a major component of the bacterial cell wall, on day 15 of pregnancy, or 150 µg/kg LPS on days 15, 17, and 19 of pregnancy leads to decreased immunostaining for oligodendrocyte (OLG)-specific proteins within the white matter of rat pups, suggesting OLG loss (Bell and Hallenbeck, 2002; Toso et al., 2005). Administration of 300 µg/kg LPS to pregnant rats on days 19 and 20 of pregnancy via intraperitoneal injection also induces significant white matter injury in the neonatal rats (Rousset et al., 2006). Pang et al., 2005 inoculated live *E. coli* to the uteri of pregnant rats on day 17 of pregnancy, and found significant apoptosis and hypomyelination in periventricular white matter of pups born to *E. coli*-treated dams as compared to those born to vehicle-treated dams (Pang et al., 2005). Furthermore, administration of LPS into pregnant sheep at mid or late gestation leads to white matter damage in fetal sheep (Mallard et al., 2003; Svedin et al., 2005). Collectively, experimental studies using different animal model systems have provided direct evidence that maternal bacterial infection significantly influences fetal brain development and may lead to the development of CP in the offspring.

Cytokines as mediators for the development of CP

Besides their immunological roles, cytokines have been recognized as important regulators of brain development (Mehler and Kessler, 1997). For example, IL-1β has a significant influence on neuronal survival (Marx et al., 2001), neuronal differentiation (Ling et al., 1998), dendrite development (Gilmore, 2004), and synaptic plasticity (Schneider et al., 1998). IL-6 has been found to affect neuronal survival (Marx et al., 2001) and dentrite development (Gilmore, 2004). There is also evidence that TNF-α is involved in the regulation of neurite growth (Neumann et al., 2002), neuronal survival (Yang et al., 2002), and hippocampal morphogenesis (Golan et al., 2004b). Furthermore, treatment with TNF-α, IL-1β, or IFN-γ induces death of both oligodendrocyte precursor cells (OPCs) and mature oligodendrocytes (OLGs) (Cai et al., 2004; Feldhaus et al., 2004; Nakazawa et al., 2006; Takahashi et al., 2003), and inhibits the differentiation of OPCs (Feldhaus et al., 2004; Vela et al., 2002). Taken together, the inflammatory cytokines play important roles during brain development. In agreement, transgenic mice over expressing IL-6 or TNF-α in the central nervous system develop a spectrum of cellular alterations resulting in pronounced neurological diseases (Wang et al., 2002). Therefore, the inflammatory cytokines have been hypothesized to mediate the development of CP following maternal bacterial infection.

Supporting evidence for the neuroinflammatory hypothesis comes from several areas of research as described below. Firstly, the neonates born with funisitis, a histological marker for fetal inflammatory systemic response, have a higher risk to develop neurological defects includeing cerebral palsy (Romero et al., 2007). Furthermore, white matter damage is frequently associated with activation of microglia, the resident immune cells in the brain (Deguchi et al., 1996). At the molecular level, an increased level of IL-18 in umbilical blood has also been found to correlate with white matter damage in preterm infants (Hagberg et al., 2005), and increased levels of TNF-α, IL-1β, and IL-6 has been found to be associated with white matter damage in cerebral palsy patients (Deguchi et al., 1996; Yoon et al., 2003). Additionally, a single nucleotide G – A base pair substitution at nucleotide -308 relative to the transcriptional start site, a poly-

morphism associated with higher level of TNF-α expression, has been reported to be associated with an increaseed risk of cerebral palsy in a recent case-control study using DNA samples collected from newborn infants with cerebral palsy as compared to control infants (Gibson et al., 2006). Secondly, experimental studies using animal model systems have found that maternal exposure to bacteria or bacterial products induces inflammation in maternal and fetal tissues (for details, see Table 2). Maternal exposure to LPS has been shown to activate microglial cells in the periventricular region of the offspring rabbits (Kannan et al., 2007), induce the production of TNF-α, IL-1β, and IL-6 in the placenta (Ashdown et al., 2006; Beloosesky et al., 2006; Urakubo et al., 2001), increase the level of IL-6 in the amniotic fluid (Beloosesky et al., 2006; Urakubo et al., 2001), and elevate the level of IL-1β in the fetal plasma of rodents (Ashdown et al., 2006). There is evidence that the cytokines produced by maternal tissues may cross placenta, enter fetal tissue (Dahlgren et al., 2006; Kent et al., 1994), and stimulate fetal immune cells to produce more cytokines (Hebra et al., 2001). After crossing blood brain barrier (Banks, 2005), these cytokines may activate astrocytes and microglia cells, which, in turn, produce more inflammatory cytokines in the fetal brain (McLaurin et al., 1995). Therefore, it is very likely that the increased levels of inflammatory cytokines in the maternal tissue could transfer maternal inflammation to the fetal brain. Furthermore, increased levels of TNF-□ and IL-1β in the fetal brain have been found to be associated with prenatal LPS-induced white matter damage (Bell and Hallenbeck, 2002; Rousset et al., 2006) while microglial activation is associated with intrauterine *E. coli*-induced PVL and OLG loss in the offspring rodents (Pang et al., 2005). Lastly, treatment with IL-10, an anti-inflammatory cytokine, suppresses intrauterine *E. coli*-induced microglial activation in the fetal brain, reduces apoptosis in the white matter, and protects the fetal brain from white matter damage in rodents (Pang et al., 2005; Rodts-Palenik et al., 2004) (for details, see Table 2). These findings provide strong support that maternal bacterial infection induced inflammatory cytokines contribute to the development of CP in the offspring.

Oxidative stress as a mediator for the development of CP

The reactive oxygen species (ROS), such as oxygen ions, free radicals and peroxides, induced by bacteria infection plays an important protective role in destroying the infecting microorganisms (Lin et al., 2005; Sakaguchi and Furusawa, 2006; Santos et al., 2007). However, oxidative stress results when the ability of the endogenous antioxidant system is overcome by the generation of ROS, and ROS will modify the nucleic acids, lipids, and proteins, which ultimately leads to cellular damage and cell death (Hald and Lotharius, 2005; Mehlhase et al., 2000). There is increasing evidence that oxidative stress is involved in the development of maternal bacterial infection-induced white matter damage and CP in the offspring. Firstly, examinations of the autopsy brain tissues have found that PVL brains exhibit increased lipid peroxidation in OPCs than non-PVL control brains (Haynes et al., 2003). Clinical studies have also found that CP patients exhibit increased lipid peroxidation and decreased antioxidant capacity as compared to healthy controls (Aycicek and Iscan, 2006). Secondly, there is accumulating evidence that oxidative stress regulates the survival and differentiation of both neuronal and glial cells (Loh et al., 2006; Mahadik et al., 2006; Wang et al., 2004). For example, intracellular depletion of GSH or cysteine leads to ROS accumulation and death of both OPCs and mature OLGs (Wang et al., 2004). Furthermore, OPCs have been found to be more susceptible to oxidative stress induced by intracellular depletion of GSH or cysteine than mature OLGs due to the presence of stronger antioxidant defense mechanisms in mature OLGs (Back et al., 1998; Wang et al., 2004). Finally, experimental animal studies have shown that maternal exposure to LPS potentiates the release of hydroxyl radicals in the brain of pups (Cambonie et al., 2004), increases protein carbonylation, and decreases the ratio of reduced/oxidized forms of glutathione (GSH/GSSG) in the hippocampus of the offspring, suggesting the presence of oxidative stress (Lante et al., 2007) (for details, see Table 3). Furthermore, pre-treatment with antioxidants, such as ascorbic acid and melatonin, significantly decreases prenatal LPS-induced fetal mortality (Chen et al., 2006a; Chen et al., 2006b), diminishes prenatal LPS-induced damages in the hippocampus of the offspring (Lante et al., 2007), and prevents prenatal LPS-induced degeneration of OPCs and hypomyelination in the fetal rat brains (Paintlia et al., 2004). More recently, it has been reported that NAC treatment prevents prenatal LPS-induced decrease of GSH content in the hippocampus, and protects prenatal LPS-induced deficits in long-term potentiation and spatial learning in the offspring (Lante et al., 2008) (for details, see Table 3). Additionally, the ROS pathway may cross-talk with the inflamematory cytokine cascade. For example, NAC has been found to attenuate prenatal LPS-induced expression of inflammatory cytokines, such as TNF-α and IL-1β, in fetal brains, and block the induction of IL-6 in maternal serum and amniotic fluid of rodents following prenatal exposure to LPS (Beloosesky et al., 2006; Paintlia et al., 2004). Taken together, these data suggest that maternal bacterial infection-induced oxidative stress contribute to the genesis of CP in the offspring.

Management of CP

Cerebral palsy patients may exhibit a spectrum of pathologies and clinical phenotypes depending on the extent and location of brain damage. Current strategies for the health care of children with CP include promoting optimal function, fostering the acquisition of new skills, and pre-

Table 1. Reported experimental animal studies to demonstrate the association between prenatal bacterial infection and brain injury.

Bacteria or bacterial products used	Host	Route of treatment	Dose of treatment	Time of treatment	Major Findings	Reference
E. coli LPS serotype O111:B4	Lewis and Fischer 344 rats	i.c.	0.1, 0.2, 0.5, 1, 3 mg/kg maternal weight	day 15 of pregnancy	Intracervical LPS treatment induces dose-dependent fetal mortality. Treatment with 0.1 mg/kg LPS decreases immunohistochemical staining of oligodendrocyte markers within the corpus callosum in the P21 offspring.	(Bell and Hallenbeck 2002)
E. coli LPS serotype O55:B5	Sprague-Dawley rats	i.p.	4 mg/kg or 0.5 mg/kg maternal weight	day 18 of pregnancy	Maternal treatment with 4 mg/kg LPS increases the expression of TNF-α and IL-1β mRNA in the fetal brain; Treatment with 0.5 mg/kg LPS on days 18 and 19 of pregnancy increases glial fibrillary acidic protein-positive astrocytes and decreases myelin basic protein staining in the brain of neonatal rats.	(Cai et al. 2000)
E. coli K1	New Zealand White rabbits	i.u.	$5x10^3$ ~ $5x10^5$ CFU	between 24 and 30 d of gestation	*E. coli* intrauterine inoculation increase cell death and white matter damage in the periventricular region of surviving fetuses.	(Debillon et al. 2000)
E. coli LPS serotype O55:B55	Sheep fetus	Fetal i.v.	1 μg/kg estimated fetal weight	day 91 of pregnancy, (3-5 injections over 5days)	Neuroinjury is found 10-11 days following initial LPS injection	(Duncan et al. 2002)
Gardnerella vaginalis	New Zealand White rabbits	i.u.	$2x10^4$ ~ $2x10^6$ CFU	day 20 or 21 of pregnancy	*G. vaginalis* intrauterine inoculation results in amnionitis and deciduitis, which is associated with increased fetal mortality, reduced birth weight, and increased brain injury in the offspring.	(Field et al. 1993)
E. coli LPS serotype O55:B5	Dunkin-Hartley guinea pig	i.p.	1, 5, 25, 50, 100, 200, 300 μg/kg maternal weight	70% gestation	Maternal LPS treatment elicits a dose-dependent cell death in the brain of the fetus 7 days following injection.	(Harnett et al. 2007)
E. coli LPS serotype O111:B4	Sheep fetus	Fetal i.v.	100 ng/kg estimated fetal weight	midgestation	Fetal LPS treatment results in focal inflammatory infiltrates and cystic lesions in periventricular white matter in 40% of the offspring.	(Mallard et al. 2003)
E. coli	Sprague-Dawley rats	i.u.	$1x10^6$ CFU	Day 17 of pregnancy	*E. coli* treatment leads to significant apoptosis in periventricular white matter of P0 pups. Treatment with IL-10 reduces *E. coli*-induced white matter damage.	(Pang et al. 2005)
E. coli LPS serotype -O55:B5	Wistar rats	i.p.	300 μg/kg maternal weight	days 19 and 20 of pregnancy	Maternal LPS treatment elevates IL-1β mRNA level in the brain of P1 offspring, and increases cell death in the brain of P1 and P7 offspring.	(Rousset et al. 2006)

Table1. Continued

E. coli LPS serotype O55:B4	Sheep fetus	Fetal i.v.	88.7 ng/kg estimated fetal weight	65% or 85% of gestation	Fetal LPS treatment leads to white matter damage, increased microglia activation, and loss of neurofilament staining in the brain of the infants.	(Svedin et al. 2005)
E. coli LPS serotype O111:B4	Fischer 344 rats	i.c.	150 µg/kg LPS maternal weight	days 15, 17, and 19 of pregnancy	Maternal LPS treatment decreases the staining of myelin proteolipid protein, a maker for oligodendrocytes, and causes sensory-motor delays in the offspring.	(Toso et al. 2005)
E. coli	New Zealand White rabbits	i.u.	10^3 ~ 10^4 CFU	days 20 or 21 of pregnancy	*E. coli* intrauterine inoculation results in fetal white matter damage.	(Yoon et al. 1997)

Abbreviations: IL: interleukin; TNF: tumor necrosis factor; i.p.: intraperitoneal; i.u.: intrauterine; i.v.: intravenous; P1: postnatal day 1.

Table 2. Reported experimental animal studies to demonstrate the association between prenatal bacterial infection-induced inflammation and brain injury.

Bacteria or bacterial products used	Host	Route of treatment	Dose of treatment	Time of treatment	Major Findings	Reference
E. coli LPS serotype O111:B4	Sprague-Dawley rats	i.p.	50 µg/kg maternal weight	day 18 of pregnancy	Maternal LPS treatment increases the levels of TNF-α, IL-1β, and IL-6 in maternal plasma and placenta, and elevates the level of IL-1β in fetal plasma.	(Ashdown et al. 2006)
E. coli LPS serotype O55:B5	Sprague-Dawley rats	i.p.	4 mg/kg Or 0.5 mg/kg maternal weight	day 18 of pregnancy	Maternal treatment with 4 mg/kg LPS increases the expression of TNF-α and IL-1β mRNA in the fetal brain; Treatment with 0.5 mg/kg LPS on days 18 and 19 of pregnancy increases glial fibrillary acidic protein-positive astrocytes and decreases myelin basic protein staining in the brain of neonatal rats.	(Cai et al. 2000)
E. coli LPS serotype O55:B5	C3H/HeN mice	i.p.	50 µg/kg maternal weight	day 15 of pregnancy	Maternal LPS treatment increases the levels of TNF-α, IL-6, and IL-1α in the maternal serum, and elevates the levels of IL-6 and IL-1α in the amniotic fluid.	(Fidel et al. 1994)
Gardnerella vaginalis	New Zealand White rabbits	i.u.	$2x10^4$ ~ $2x10^6$ CFU	days 20 or 21 of pregnancy	*G. vaginalis* intrauterine inoculation results in amnionitis and deciduitis, which is associated with increased fetal mortality, reduced birth weight, and increased brain injury in the offspring.	(Field et al. 1993)
E. coli LPS serotype O111:B4	Sprague-Dawley rats	i.p.	0.1 mg/kg maternal weight	day 18 of pregnancy	Maternal LPS treatment increases corticotropin-releasing factor in the fetal brain, elevates TNF-α, IL-6, and IL-10 in the chorioamnion, and upregulates TNF-α, IL-1β, and IL-6 in the placenta.	(Gayle et al. 2004)

Table 2. Continued.

E. coli LPS	Black c-57 mouse	i.p.	0.12 µg/g maternal weight	day 17 of pregnancy	Maternal LPS increases expression of IL-6 in the fetal brain; and impairs distinct aspects of learning and memory in the adult offspring.	(Golan et al. 2005)
Salmonella enteritidis LPS, or Rc mutant *E. coli* LPS	Sprague-Dawley rats	i.p.	50 µg/kg maternal weight	day 19 of pregnancy	Maternal LPS treatment increases plasma TNF-α concentration in both dams and their fetuses, and induces endotoxin tolerance in P0 offspring.	(Goto et al. 1997)
E. coli LPS serotype O127:B8	New Zealand White rabbits	i.u	20 and 30 µg/kg maternal weight	day 28 of pregnancy	Maternal LPS treatment leads to dose-dependent activation of microglia in the offspring at postnatal day (P)1.	(Kannan et al. 2007)
E. coli LPS serotype O127:B8	C57BL6/J mice	i.p.	50 µg per mouse	day 18 of pregnancy	Maternal LPS treatment increases the expression of MCP-1, IL-6, IL-1β, and VEGF in fetal brain.	(Liverman et al. 2006)
E. coli LPS serotype O111:B4	Sheep fetus	Fetal i.v.	100 ng/kg estimated fetal weight	midgestation	Fetal LPS treatment results in focal inflammatory infiltrates and cystic lesions in periventricular white matter in 40% of the offspring.	(Mallard et al. 2003)
E. coli	Sprague-Dawley rats	i.u.	$1x10^6$ CFU	day 17 of pregnancy	*E. coli* treatment leads to microgial activation, astrogliosis, and apoptosis in periventricular white matter of the offspring. Treatment with IL-10 reduces *E. coli*-induced white matter damage.	(Pang et al. 2005)
E. coli	Sprague-Dawley rats	i.u.	1×10^7 CFU	day 17 of pregnancy	IL-10 treatment decreases LPS-induced oligodendrocyte loss, white matter damage, and apoptosis in the neonatal brain.	(Rodts-Palenik et al. 2004)
E. coli LPS serotype -O55:B5	Wistar rats	i.p.	300 µg/kg maternal weight	days 19 and 20 of pregnancy	Maternal LPS treatment elevates IL-1β mRNA level in the brain of P1 offspring, and increases cell death in the brain of P1 and P7 offspring.	(Rousset et al. 2006)
E. coli LPS serotype O127:B8	CD-1 mice	i.u.	10 µg per mouse	day 15 of pregnancy	Maternal LPS increases the levels of TNF-α, IL-1β, IL-6, and IL-10 in the amniotic fluid. Inhibition of PDE4 by rolipram prevents LPS-induced rise of inflammatory cytokines, preterm delivery, and fetal demise.	(Schmitz et al. 2007)
E. coli LPS serotype O55:B4	Sheep fetus	Fetal i.v.	88.7 ng/kg estimated fetal weight	65% or 85% of gestation	Fetal LPS treatment leads to white matter damage, increased microglia activation, and loss of neurofilament staining in the brain of the infants.	(Svedin et al. 2005)
E. coli LPS serotype O55: B5	Sprague-Dawley rats	i.p.	0.5 or 2.5 mg/kg maternal weight	day 18 of pregnancy	Maternal treatment with 0.5 mg/kg LPS increases the levels of TNF-α, IL-1β and IL-6 in the placenta. Maternal treatment with 2.5 mg/kg LPS increases TNF-α, IL-1β, and IL-6 in the placenta.	(Urakubo et al. 2001)

Abbreviations: IL: interleukin; TNF: tumor necrosis factor; i.p.: intraperitoneal; i.u.: intrauterine; i.v.: intravenous; MCP: monocyte chemoattractant protein; P1: postnatal day 1; PDE: phosphodiesterase.

Table 3. Reported experimental animal studies to demonstrate the association between prenatal bacterial infection induced-oxidative stress and brain injury.

Bacteria or bacterial products used	Host	Route of treatment	Dose of treatment	Time of treatment	Major Findings	Reference
E. coli LPS serotype O111:B4	Sprague-Dawley rats	i.p.	100 µg/kg maternal weight	day 18 of pregnancy	Maternal LPS treatment increases the levels of IL-6 and IL-10 in maternal serum, and elevates the level of IL-6 in the amniotic fluid and placenta, which could all be attenuated by N-acetyl cysteine (NAC) treatment.	(Beloosesky et al. 2006)
E. coli LPS serotype O55:B5	Sprague–Dawley rats	i.p.	500 µg/kg maternal weight	day 19 of pregnancy	Maternal LPS treatment increases protein carbonylation in male fetal brain, and leads to impaired spatial recognition in the offspring.	(Lante et al. 2007)
E. coli LPS serotype O55:B5	Sprague–Dawley rats	i.p.	500 µg/kg maternal weight	day 19 of pregnancy	NAC treatment prevents LPS-induced decrease of GSH content in the hippocampus, and protects LPS-induced deficits in long-term potentiation and spatial learning.	(Lante et al. 2008)
E. coli LPS serotype O55:B5	Sprague-Dawley rats	i.p.	1, 2, or 4 mg/kg maternal weight	day 18 of pregnancy	NAC protects LPS-induced fetal mortality, attenuates LPS-induced expression of TNF-α, IL-1β, and iNOS in fetal rat brains, and inhibits LPS-induced hypomyelination.	(Paintlia et al. 2004)

Abbreviations: i.p.: intraperitoneal; NAC: N-acetyl cysteine.

preventing and/or treating the complications of CP (Gibson et al., 2007; Jones et al., 2007a). Several regimens to manage the musculoskeletal motor deficit, a key sign of CP, have been reported. Orthopedic surgery is sometimes used to correct and/or prevent musculoskeletal deformities (Jones et al., 2007a). As an alternative or supplement to orthopedic surgery, botulinum toxin type A (BTX-A), a neurotoxin produced by the bacterium *Clostridium botulinum* that blocks the release of acetyl cholinesterase, has been reported to decrease spasticity and improve conscious movements such as crawling, standing, walking at 3 – 24 weeks following BTX-A injection (Bjornson et al., 2007; Gibson et al., 2007; Meholjic-Fetahovic, 2007). Hyperbaric oxy-gen treatment (HBOT) and pressurized room air have been shown to improve motor function, yet adverse effects including seizure has also been reported during HBOT treatment (McDonagh et al., 2007). Medications, such as Baclofen, have also been shown to improve motor function and reduce spasm-related pain (Jones et al., 2007a). In general, no single treatment method has proven to be sufficient alone and a combination of medi-cal treatments and physical therapy are often carefully designed to manage the motor deficits in CP (Jones et al., 2007a).

DISCUSSION

Normal brain development involves precisely timed cellular and molecular events including cell proliferation, migration, differentiation, myelination, and synaptogenesis (Holmes and McCabe, 2001). For example, OPCs primarily arise from the neuroepithelium of the subventricular zone in mid-late to late gestational and early postnatal mammalian brain, and migrate to the developing white matter. After they reach appropriate axons, OPCs exit the cell cycle and differentiate into myelin-forming OLGs (Baumann and Pham-Dinh, 2001; Simons and Trajkovic, 2006). All these processes could potentially be affected by environmental and genetic factors. In order to ensure full and timely myelination of all axonal tracts, the process and timing of oligodendrogenesis, migration, and differentiation must be tightly controlled and coordinated with neurogenesis and neuronal differentiation (Simons and Trajkovic 2006). However, bacterial infection during pregnancy elevates the expression of inflammatory cytokines and increases the formation of ROS in the fetus, which significantly affects the survival, differentiation, maturation trajectory of OPCs, as well as the survival of mature OLGs (Back et al., 1998; Bell and Hallenbeck, 2002; Feldhaus et al., 2004; Wang et al., 2004), leading to OLG loss and subsequently hypomyelination, one of the hallmarks of CP. Consistently, many experimental

studies have reported white matter damage induced by maternal bacterial infection occurring at mid-late gestation, late gestation, and early postnatal periods when most of the oligo-dendrogenesis occurs (Back et al., 1998; Levine et al., 1993; Thomas et al., 2000).

It should be emphasized that besides the effects of inflammatory cytokines and oxidative stress, other mechanisms such as increased maternal temperature and fetal hypoxia during maternal bacterial infection may also contribute to fetal brain damage and the development of CP (Coumans et al., 2005; Dalitz et al., 2003). For example, heat stress during gestation has been reported to produce seizures, abnormal writhing movements of the limbs and body, and other gross abnormalities in the central nervous system in experimental animal models (Edwards, 2006; Mottola et al., 1993) while maternal hypoxia has been found to cause white matter damage in the offspring rabbits (Derrick et al., 2007), and reduce cerebral cortex cell density and cell size in mouse (Golan et al., 2004a). Understanding the mechanistic links between maternal bacterial infection and the development of CP in the offs-pring could potentially lead to novel and effective
therapeutic strategies.

Conditions such as periodontal disease (Felice et al., 2005), bacterial vaginosis (Oakeshott et al., 2004; Ugwumadu, 2002), and chlamydia (Hou et al., 2006) are some possible scenarios for pregnant women to contract bacterial infection. Overall, the susceptibility and extent of white matter damage during maternal bacterial infection is affected by a combination of genetic factors, severity of the infection, strain and virulence of the infecting microorganism, developmental period of the offspring when bacterial infection occurs, and the existence of any additional environmental factors during prenatal and early postnatal period (Back, 2006; Levine et al., 1993; Meyer et al., 2006; Thomas et al., 2000). Experimental animal models will be useful to thoroughly dissect the mechanisms underlying maternal bacterial infection-induced neurodevelopmental deficits and to examine the neurological defects following maternal exposure to multiple insults.

Conclusion

Maternal bacterial infection is one important prenatal factor that could lead to white matter damage and utimattely CP in the offspring. Inflammatory cytokines and ROS induced during maternal bacterial infection significantly influence fetal brain development and contribute to the development of CP in the offspring.

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