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Sihao Diao [a,b,c], Chao Chen [b,c], Alexandre Benani [d], Christophe Magnan [e], Juliette Van Steenwinckel [a], Pierre Gressens [a], Céline Cruciani-Guglielmacci [e], Alice Jacquens [a,f,1], Cindy Bokobza [a,*,1]

[a] Université Paris Cité, Inserm, NeuroDiderot, 75019, Paris, France
[b] Department of Neonatology, Children's Hospital of Fudan University, Shanghai, 201102, China
[c] Key Laboratory of Neonatal Diseases, National Health Commission, China
[d] CSGA, Centre des Sciences du Goût et de l'Alimentation, UMR 6265 CNRS, INRAE, Institut Agro Dijon, Université Bourgogne Franche-Comté, Dijon, France
[e] Université Paris Cité, BFA, UMR 8251, CNRS, F-75013, Paris, France
[f] Department of Anesthesia and Critical Care, APHP-Sorbonne University, Hôpital La Pitié- Salpêtrière, Paris, France

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ABSTRACT

Preterm birth and its related complications have become more and more common as neonatal medicine advances. The concept of "developmental origins of health and disease" has raised awareness of adverse perinatal events in the development of diseases later in life. To explore this concept, we propose that encephalopathy of prematurity (EoP) as a potential pro-inflammatory early life event becomes a novel risk factor for metabolic diseases in children/adolescents and adulthood. Here, we review epidemiological evidence that links preterm birth to metabolic diseases and discuss possible synergic roles of preterm birth and neuroinflammation from EoP in the development of metabolic diseases. In addition, we explore theoretical underlying mechanisms regarding developmental programming of the energy control system and HPA axis.

1. Introduction

Obesity has become a global health issue over the last several decades, affecting adults as well as children and adolescents. The prevalence of obesity has increased in not only high-income countries but also low-income and middle-income countries (Collaboration, 2017; Jebeile et al., 2022). The World Health Organization estimated that more than 650 million adults were obese and that over 340 million children/adolescents were overweight or obese in 2016 (WHO). Excess abdominal fat accumulation can contribute to an increased risk of metabolic syndrome (MetS), cardiovascular disease, and several types of cancer (Després et al., 2006; Powell-Wiley et al., 2021; Avgerinos et al., 2019). MetS is a clustering of metabolic disease risk factors that includes abdominal adiposity, dyslipidemia, insulin resistance, and hypertension. MetS is also associated with a significant risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease (Cornier et al., 2008). Understanding the causes or risk factors of metabolic diseases would improve corresponding medical or political actions. Such causes and risk factors are often influenced by the bio-socioecological framework, in which individual susceptibility and socioeconomic/environmental factors interact (Jebeile et al., 2022; Safaei et al., 2021). Evidence that multiple perinatal factors (*i.e.,* maternal obesity, intrauterine growth restriction) can lead to metabolic disease in adulthood underscores the importance of early life events in the onset of these conditions (Desai et al., 2020; Hoffman et al., 2021).

Preterm birth is defined as a livebirth before 37 gestational weeks (Moutquin, 2003). The burden of prematurity has been increasing worldwide: in 2014, 14.84 million neonates were born prematurely, 10.6 % of the global birth rate (Chawanpaiboon et al., 2019). The etiology of preterm birth is multifactorial and complex. Most are spontaneous, with undefined causes and risk factors, but some can result from maternal or fetal medical issues (Vogel et al., 2018). As the major organ systems of preterm infants are still developing and highly vulnerable to antenatal and postnatal insults relative to those of term infants, they are more likely to encounter a wide range of complications and their long-term consequences (Walani, 2020). For example, although the survival rate of extremely preterm infants has improved due to developing neonatal medical care, major morbidity, including brain lesions,

* Corresponding author. Inserm Unité 1141, Hôpital Robert Debré, 48 Boulevard Sérurier, 75019, Paris, France.
E-mail address: cindy.bokobza@inserm.fr (C. Bokobza).
[1] Contributed equally.

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bronchopulmonary dysplasia, and necrotizing enterocolitis, has been shown to be more common in preterm survivors (Zhu et al., 2021). Ongoing research has focused on exploring the long-term outcomes of preterm birth with complications and underlying mechanisms.

In this review, we introduce prematurity as a potential risk factor for metabolic diseases under the concept of "Developmental Origins of Health and Disease" (DOHaD). We focused on current epidemiological evidence of the association between preterm birth and metabolic diseases. Encephalopathy of Prematurity (EoP) described the constellation of white and grey matter lesions associated with mild to severe cognitive impairments. We propose EoP as a possible adverse perinatal event to be a novel risk factor for metabolic diseases later in life. Moreover, we discuss the possible underlying mechanisms in terms of the connections between the CNS and peripheral metabolism: 1) EoP-induced neuroinflammation disturbs energy homeostasis; 2) preterm birth and/or inflammation affect hypothalamic-pituitary-adrenal (HPA) axis activities.

2. Developmental programming of metabolic diseases

The concept of DOHaD originated from an epidemiological study of infant and adult disease mortality in 1986 (Barker et al., 1986). Barker et al. conducted a study spanning 1968–1978, revealing a strong correlation between infant mortality (1921–1925) and later adult ischemic heart disease. Their findings suggest a link between high neonatal mortality, undernutrition in pregnancy, and low birth weight in economically disadvantaged areas, leading to increased adult mortality in the 1970s (Barker et al., 1986). These findings subsequently led to the theory that environmental exposure at a young age can have a major impact on long-term health and the development of disease (Barker, 2007). The heightened awareness of perinatal stigma and events in metabolic disease research underscores the impact of maternal factors (obesity, T2DM, gestational diabetes mellitus, poor nutrition, …) in promoting the consequences of metabolic dysfunction in descendants (Hillier et al., 2007; Fraser et al., 2010; Hochner et al., 2012). Neonates with a low birth weight show "catch-up" growth during the first few years of life to compensate for the lack of fetal nutrition/growth and have an increased risk of metabolic dysregulation (Crispi et al., 2010; Black et al., 2013; Ong et al., 2000). The underlying long-term mechanisms of developmental malnutrition on metabolism are not yet fully known; however, accumulating evidence increasingly points to inflammatory processes as significant drivers of metabolic adults dysfunctions. Diet-induced inflammation is crucial in metabolic diseases (Catalano et al., 2017; Ramsay et al., 2002), activating the immune system in peripheral organs, disrupting metabolic homeostasis (reviewed in (Saltiel et al., 2017; Rohm et al., 2022; Lee et al., 2021)). Neuroinflammation, triggered by diet, affects the hypothalamus, influencing food intake and energy expenditure (Thaler et al., 2012). Simultaneously, diet-induced stress hyperactivates the HPA axis, causing energy imbalance and insulin resistance [reviewed in (Janssen, 2022)].

Since up to 40 % preterm deliveries are associated with maternal or fetal infection/inflammation (Barros et al., 2015; Nadeau et al., 2016), we hypothesize that preterm birth with/without EoP share similar mechanisms as adult malnutrition on the onset of metabolic diseases. In the central nervous system (CNS), prematurity and/or neuroinflammation could disturb energy homeostasis and HPA axis activities, resulting in long-term metabolic consequences.

3. Preterm birth is associated with the development of metabolic diseases

3.1. Preterm birth and obesity

A number of cohort studies have suggested that preterm birth is significantly associated with a greater risk of obesity in children/adolescents. Prematurity may lead to early onset and ongoing obesity in adulthood. In US pediatric clinics, researchers found an increasing percentage of obese children/adolescents with age (from approximately 20% at the age of 3–5 years to more than 35% at the age of 15) in the population who were born prematurely. These obese adolescents showed a higher body mass index (BMI) at the age of 24 months (Vasylyeva et al., 2013).

Various subcategories of prematurity in obesity have also been studied. Based on gestational age, preterm birth can be divided into extremely preterm birth (<28 weeks), very preterm birth (28–32 weeks), and moderate/late preterm birth (32–37 weeks) (Quinn et al., 2016). Over the past several years, extremely preterm infants have gradually become the focus of research because of their high mortality and complex morbidity (Usuda et al., 2022). Indeed, they have a very high risk of various insults. One study found that 22% of extremely preterm children had a BMI over the 85th percentile and 10% had a BMI over the 95th percentile around the age of 6–7 years (Vohr et al., 2018). Similar results have also been reported for late preterm birth: adolescents who were born from 34 to 36 gestational weeks had a higher BMI than their peers born at term (Hui et al., 2015). The observed accelerated postnatal growth was closely associated with childhood obesity in both the extremely preterm and late preterm children in these studies. Notably, early term birth (37–38 gestational weeks) is also associated with a more common incidence of being overweight/obese, as well as other metabolic diseases, among adolescents than those born at term (39–40 gestational weeks) (Paz Levy et al., 2017).

This emphasizes the presence of a wide window of perinatal vulnerability to metabolic diseases. Furthermore, several studies have investigated abdominal adiposity in addition to BMI. The waist circumference or waist-hip/waist-height ratio is higher, along with BMI, among obese children, regardless of the prematurity subcategory, suggesting that central obesity may be the dominant type of obesity in this setting (Vohr et al., 2018; Hui et al., 2015). A meta-analysis that included 602 preterm adults showed an association between prematurity and higher body fat mass in adults (Markopoulou et al., 2019). Overall, numerous studies conducted in different regions of the world all showed that preterm birth contributes to abdominal obesity in children/adolescents. This is possibly due to altered metabolism-related development and accelerated postnatal growth to compensate for the relative lack of in utero growth.

3.2. Preterm birth and metabolic syndrome

Preterm birth may also lead to an increased risk of MetS components other than central obesity in later life. For example, adults born prematurely show higher fasting glucose and insulin levels than their peers born at term (Markopoulou et al., 2019). More interestingly, the disrupted insulin homeostasis observed in preterm-born adults can be traced back to altered insulin levels both at birth and at school age, suggesting that the abnormal insulin levels present in preterm-born adults may originate from early metabolic developmental programming (Wang et al., 2014; Finken et al., 2006). Previous studies have also supported the relationship between preterm birth and hypertension. Arterial blood pressure, including systolic and diastolic blood pressure, was shown to be higher when assessed at two years of age and in adulthood (Markopoulou et al., 2019; Heidemann et al., 2019). These dysregulated factors may have a significant impact on the development of T2DM and cardiovascular disease.

3.3. Preterm birth and diabetes

The adverse effects of preterm birth are involved in both pancreatic β cell dysfunction and insulin resistance, leading to type 1 diabetes mellitus (T1DM) and T2DM. Several large cohorts and meta-analyses have shown that preterm birth is inversely associated with an increased risk of T1DM and T2DM (Crump et al., 2020; Kajantie et al., 2010; Li et al., 2014). In a recent Swedish cohort of over 400 million people, preterm

birth contributed to an approximately 1.2-fold higher risk of T1DM before the age of 18 years and a 1.5-fold higher risk of T2DM at the age of 18–43 years than for those born at term (Crump et al., 2020). Preterm birth may alter normal pancreatic maturation during the last trimester and result in a permanent lack of insulin production in pancreatic β cells. A smaller β cell mass and reduced insulin release that persisted to adulthood were, indeed, found in preterm lambs (Bansal et al., 2015). Surprisingly, hyperglycemia in premature infants is commonly attributed to insufficient pancreatic development rather than monogenic neonatal diabetes. However, a study in 2016 brought attention to the fact that patients with neonatal diabetes resulting from a monogenic cause can be born preterm, particularly those with 6q24 abnormalities or *GATA6* mutations (Besser et al., 2016).

3.4. *Encephalopathy of prematurity as a potential risk factor for metabolic diseases*

Preterm infants are exposed to an extrauterine environment at a critical phase when neural cell differentiation and maturation, axonal growth, myelination, synaptogenesis, and neurocircuit formation take place (Yates et al., 2021). The immature CNS, along with the respiratory and cardiovascular systems, is highly vulnerable to postnatal events, such as inflammation and/or infection, perinatal asphyxia, and hyperoxia, thus contributing to EoP. Evidence from human and animal models has shown white matter injury, as well as grey matter injury, in infants with EoP (Volpe, 2009). The most common form of white matter injury gradually transforms into diffuse white matter injury, resulting in the selective blockade of pre-myelinating oligodendrocyte (PreOL) maturation and the arrest of myelination (Back, 2017). On the other hand, grey matter injury is identified in the cerebral cortex, thalamus, basal ganglia, hippocampus, and cerebellum and involves neuronal dysmaturation and loss, axonal injury, abnormal synaptic activity, and impaired thalamocortical connectivity (Smyser et al., 2019; Burd et al., 2009; Volpe, 2019; Klein et al., 2022; Stolp et al., 2019; Fleiss et al., 2020; Strahle et al., 2019). A recent meta-analysis reported that EoP is responsible for long-term motor, cognitive, hearing, and visual impairment in preterm infants, indicating permanent neurofunctional injuries following EoP (Rees et al., 2022). We, thus, hypothesized that EoP may be related to metabolism-related disruption of neurodevelopment and the onset of metabolic diseases in later life, because: 1) as preterm birth is the most important and indispensable factor in the etiology of EoP, it is a significant contributor to multiple metabolic diseases, 2) EoP involves the combined hits of prematurity and a pro-inflammatory CNS and/or systemic insults, leading to a wide range of white matter and grey matter injury, and 3) EoP may result in permanent functional and structural CNS injury, resulting in multiple long-term consequences.

4. Programming effects of preterm birth on the energy control system

4.1. *Central control of energy homeostasis*

The CNS plays a vital role in maintaining energy homeostasis from energy intake to expenditure. Among the regions of the brain, the hypothalamus is particularly important for receiving and integrating metabolic signals from circulating hormones, metabolites, and nutrients; it is also responsible for the response to these messages to maintain metabolic homeostasis (Jais et al., 2022). Consisting of several hypothalamic nuclei involved in metabolic regulation, the arcuate nucleus (ARC) is a master regulator of appetite and food intake.

There are two well-studied neuronal subpopulations in the ARC that interact with each other in the regulation of feeding. The first is an orexigenic neuronal population that releases agouti-related peptide (AgRP), neuropeptide Y (NPY), or GABA (van den Top et al., 2004). The other is responsible for expressing anorexigenic pro-opiomelanocortin (POMC), which gives rise to α-melanocyte stimulating hormone (α-MSH) (Zhan et al., 2013). The interplay between AgRP/NPY and POMC neurons is affected by circulating hormones (leptin, ghrelin, insulin), leading to the regulation of energy and glucose homeostasis (Lavoie et al., 2023). AgRP and α-MSH play opposite roles via the stimulation or inhibition of the melanocortin 3 and 4 receptors in the paraventricular nucleus, whereas NPY acts on Y1/Y5 receptors (Valassi et al., 2008; Waterson et al., 2015; Nuzzaci et al., 2015). In addition, GABAergic neurons mediate the anorexigenic effects of leptin on POMC neurons (Fig. 1) (Lavoie et al., 2023). Aside from the regulatory role in food intake, AgRP/NPY and POMC neurons are also involved in glucose production and metabolism (Engström Ruud et al., 2020; Steculorum et al., 2016; Xu et al., 2018). Non-neuronal cell populations, such as microglia and astrocytes (described hereafter), in the hypothalamus also participate in the normal regulation of appetite and glucose metabolism (García-Cáceres et al., 2016; De Luca et al., 2019). For example, hypothalamic astrocytes can sense and control systemic glucose metabolism via insulin signaling in cooperation with POMC neurons (García-Cáceres et al., 2016). In addition, interactions between astrocytes and POMC neurons in the hypothalamus take part in the behavioral regulation of satiety (Nuzzaci et al., 2020). On a related note, a study from Israel highlighted that polymorphisms in Leptin (LEP) and its receptor (LEPR) in neonates are linked to an elevated risk of preterm birth. This

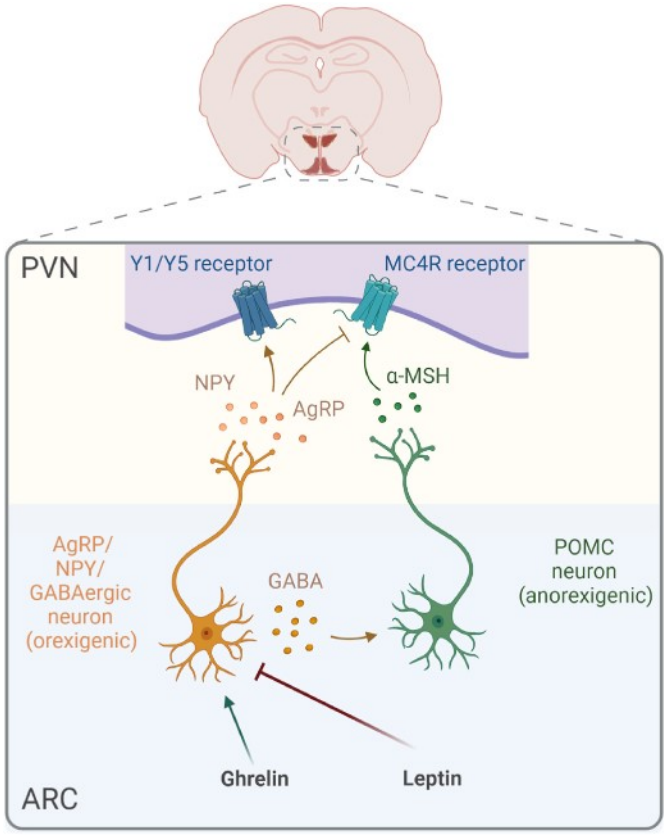

Fig. 1. Proposed model for neuronal control of appetite in the hypothalamus. In the ARC, two types of neurons play opposite roles under the direct or indirect control of circulating hormones from peripheral organs (adipose tissue, pancreas, gastrointestinal tract). Orexigenic neurons release AgRP and NPY, whereas anorexigenic neurons release α-MSH derived from POMC. These neuropeptides then act on different receptors of neurons in the PVN to regulate appetite. AgRP inhibits MC4Rs to increase appetite, whereas α-MSH acts as a stimulator of MC4Rs to suppress appetite. On the other hand, NPY positively regulates food intake via activation of the Y1/Y5 receptor in the PVN. Abbreviations: ARC, arcuate nucleus; AgRP, agouti-related peptide; NPY, neuropeptide Y; α-MSH, α-melanocyte stimulating hormone; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; MC4R, melanocortin 4 receptor.

underscores evenmore a potential connection between molecules/receptors involved in glucose homeostasis and prematurity (Salem et al., 2016).

Development of the hypothalamus generally occurs in two steps: neurogenesis and circuit formation. In general, neurogenesis starts during the second trimester in humans and achieved before full term in humans (Markakis, 2002; Bouret, 2012). Thus, the period when preterm delivery might occur is critical for hypothalamic programming. In children/adults born preterm, there are signs of long-lasting energy imbalance and unhealthy dietary behaviors. Young adults with very low birth weight showed lower resting energy expenditure than peers born term (Sipola-Leppänen et al., 2011). They also reported unhealthier dietary preference of sweets over protein-enriched food, less dietary restraint (including less concern for dieting and less weight fluctuation) (Sharafi et al., 2016). Moreover, individual born very preterm are predicted to present adult obesity and higher insulin levels (Finken et al., 2006). It suggests the dysregulated central control of energy homeostasis following preterm birth in the long term.

4.2. Neuroinflammation in preterm birth

Preterm infants are at high risk of inflammatory perinatal events, such as intrauterine/postnatal infections, sterile inflammation, and hypoxia-ischemia. Triggered neuroinflammation is significantly associated with the pathogenesis of EoP (Hagberg et al., 2015). One of the hallmarks of neuroinflammation in EoP is reactive gliosis in white and grey matter (Back, 2017). Microglia and astrocytes are two of the primary cell types that account for glial responses to a wide range of perinatal insults and damage in the developing brain.

Microglia are derived from primitive myeloid progenitors in the embryonic yolk sac and start to take up residence in the CNS early, at 4.5 gestational weeks in humans and at embryonic day 9.5 in rodents (Ginhoux et al., 2010; Menassa et al., 2018; Li et al., 2018). In the developing brain, microglia exert critical functions in phagocytosis, synapse modulation/pruning, and myelination in a time-specific and region-dependent manner (Li et al., 2018; Matcovitch-Natan et al., 2016). For example, single-cell RNA sequencing of microglia revealed developmental heterogeneity at early postnatal period. A recently identified subset called proliferative area-associated microglia (PAM) showed less newly formed transient glial engulfment in developing white matter (corpus callosum, cerebellum) (Li et al., 2019). PAM are essential for the regulation of myelination in the developing brain.

A wide range of preclinical models in rodents and sheep with various insults, such as systemic inflammation/infection (*i.e.*, interleukin-1β (IL1β), lipopolysaccharide), hypoxia-ischemia, or hyperoxia, have been developed for the study of reactive microglia in EoP (Favrais et al., 2011; Lear et al., 2022; Schmitz et al., 2011; Vannucci et al., 1997). Regardless of the type of perinatal events, previous evidence has shown there to be several phenotypes of microglia based on their transcriptional signature of different cytokines and chemokines, exerting dynamic functions in the regulation of neuroinflammation (Van Steenwinckel et al., 2019; Bokobza et al., 2022). Klein et al. recently revealed the regional heterogeneity of reactive microglia when responding to a preclinical mouse model of EoP (systemic IL1β exposure during the perinatal period) (Klein et al., 2022). Although cerebrum and cerebellum microglia share common pathological phenotypes, as described above, significantly different expression levels among these representative transcriptional markers have been observed in microglia between the two regions. For example, cerebellar microglia have a unique type II interferon signaling profile relative to cerebrum microglia. Yet, the role of microglia in the hypothalamus is not clarified following EoP. However, it is very likely to exert functional heterogeneity in a region-specific manner.

Astrocytes are the predominant cell type in the CNS. They originate from neural precursor cells in the ventricular zone, along with neurons and oligodendrocytes (Von Visger et al., 1994). The perinatal period is critical for the development of astrocytes. Astrogenesis follows increased neurogenesis and is initiated at around embryonic day 18 in rodents, showing complex heterogeneity in different regions of the brain (Qian et al., 2000). In the developing brain, astrocytes play an important role in synaptogenesis and the metabolic and structural support of neuronal development (Ullian et al., 2001). Moreover, early immature astrocytes take part in expressing extracellular matrix molecules and neurotrophic factors, which are required for glial development (Wiese et al., 2012). During the perinatal period, astrocytes are also reactive to a broad spectrum of insults. They can express receptors for pathogen-associated molecular patterns and damage-associated molecular patterns and initiate innate immune responses to produce inflammatory chemokines and cytokines, together with microglia, when facing infection/sterile inflammation (Sofroniew, 2020). In addition, reactive astrocytes can modulate the extracellular matrix environment by regulating the levels of its components, such as those of proteoglycans and hyaluronan (Back et al., 2005; Deng et al., 2015). Overall, the interplay between astrocytes and microglia contributes to most of the neuroinflammation in EoP.

4.3. Neuroinflammation in preterm birth and its impact on energy balance

The early onset of hypothalamic inflammation, mediated by microglia and astrocytes, has been implicated in disrupting energy balance in both human and rodent studies related to obesity. Immunohistochemical staining of ionized calcium-binding adapter molecule 1 (Iba1, a microglia marker) and glial fibrillary acidic protein (GFAP, an astrocyte marker) in human postmortem samples of the mediobasal hypothalamus (MBH) provides evidence of reactive microgliosis and astrogliosis in obese patients (Baufeld et al., 2016; Schur et al., 2015). Additionally, obese patients exhibit a significantly increased T2-weighted signal from magnetic resonance imaging in the MBH compared to lean controls, indicating a relationship between gliosis and obesity in humans (Thaler et al., 2012).

In rodent models, diet-induced obesity is associated with neuroinflammation (Salvi et al., 2022), with a high-fat diet (HFD) triggering gliosis within as little as 3 h (Cansell et al., 2021). Elevated expression of pro-inflammatory cytokines (e.g., Il6, Tumor necrosis factor α) and NF-κB pathway genes (inhibitor of nuclear factor kappa B kinase) is observed in the hypothalamus, whereas peripheral tissues like the liver or adipose tissue do not show a similar increase (Thaler et al., 2012). This highlights that hypothalamic inflammation onset in obesity is acute and not driven by chronic peripheral inflammation.

Magnetic resonance imaging and histological analysis confirm that reactive gliosis, primarily involving microglia and astrocytes in the arcuate nucleus (ARC), accounts for the onset of hypothalamic inflammation. This gliosis is likely responsible for the production of pro-inflammatory chemokines and cytokines (Lee et al., 2013). Research indicates that inflammatory signaling triggered by an HFD in both microglia and astrocytes regulates energy expenditure and food intake, mediating susceptibility to obesity (Valdearcos et al., 2017; Douglass et al., 2017).

Notably, even in the absence of an HFD, forced microglia reactivation by genetic methods increases food intake and reduces energy expenditure by significantly decreasing MBH neuron sensitivity to leptin signaling (Valdearcos et al., 2017). This suggests that a neuroinflammation context similar to the one discussed can drive impairments in energy expenditure and food intake.

Moreover, similarities between early-onset preterm (EoP)-induced and diet-induced neuroinflammation include reactive microgliosis and astrogliosis in response to CNS injury or diet, pro-inflammatory pathway signaling in reactive microglia and astrocytes, and increased secretion of pro-inflammatory cytokines and chemokines (Fig. 2). Thus, we hypothesize a similar mechanism: neuroinflammation mediated by microglia and astrocytes likely presents pro-inflammatory actions within the hypothalamus, leading to disrupted energy homeostasis following EoP.

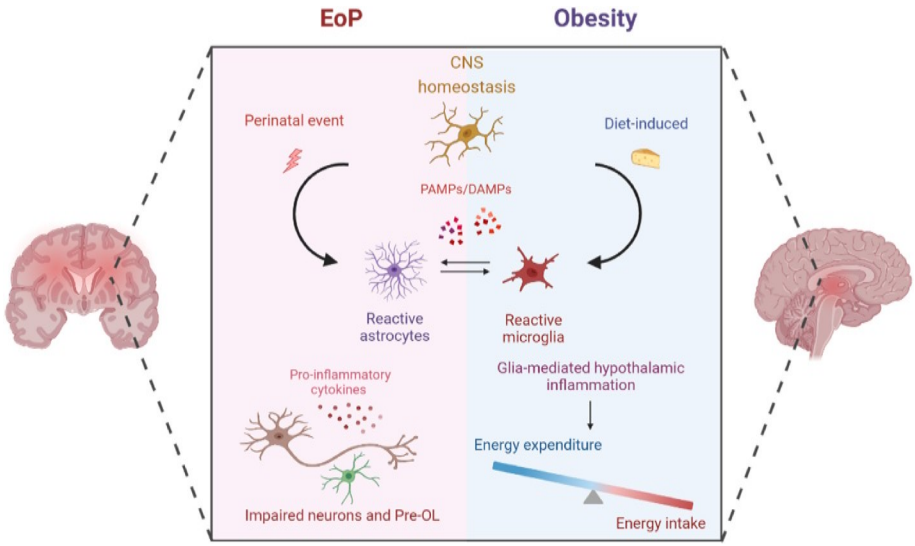

Fig. 2. Neuroinflammation triggered by EoP or diet: what are the consequences? Generally, EoP involves diffuse inflammation in the white matter, as well as grey matter, whereas diet triggers hypothalamic inflammation in the early onset of obesity. The characteristics of glial-mediated neuroinflammation in EoP and obesity are similar. Reactive gliosis and pro-inflammatory cytokines play major and vital roles, leading to two different consequences: i) impaired neurons and Pre-OLs in EoP and ii) disrupted energy balance in obesity. Abbreviations: EoP, encephalopathy of prematurity; CNS, central nervous system; PAMP, pathogen-associated molecular patterns; DAMP, damage-associated molecular patterns; Pre-OL, pre-myelinating oligodendrocyte.

5. Programming effects of preterm birth on hypothalamic-pituitary-adrenal axis

The HPA axis responds actively to physical and/or phycological stresses. It acts as the main neuroendocrine system to link the CNS with endocrine glands. The development of the HPA axis can be programmed in preterm infants due to relative immaturity. Imbalanced cortisol level can then lead to hyperglycemia, insulin resistance, and dyslipidemia (Andrew et al., 2002). Thus, it is possible that the HPA axis also participates in the development of metabolic diseases following preterm birth.

The major hypothalamic nuclei participating in the modulation of the HPA axis is PVN, where a subpopulation of neurons secrete corticotropin-releasing hormone (CRH) and vasopressin (AVP) (Bao et al., 2005). Circulating adrenocorticotropic hormone (ACTH) released by the pituitary gland in response to these neuropeptides then increases synthesis and secretion of cortisol at the adrenal cortex (Simpson et al., 1988). In turn, cortisol can mediate negative feedback by traveling to the CNS and inhibiting the release of CRH and ACTH. The development of the HPA axis starts at early gestation and continues postnatally (Goto et al., 2006).

Preterm birth, as a stressful perinatal event, exerts adverse modulations on the HPA axis regarding end-point product cortisol. Evidence shows that compared with infants born term, those born extremely preterm had a flattened salivary diurnal cortisol slope within the first year of life (Stoye et al., 2022a, 2022b). And extremely preterm infants showed a lower basal salivary cortisol level at 3 months and then increase to a higher level at 8 months and 18 months compared with full-term infants (Grunau et al., 2007). Interestingly, contrary findings are seen in infants born very preterm (Stoye et al., 2022b; Grunau et al., 2007). Moreover, a high cortisol level in extremely preterm infants was associated with the incidence of cerebral palsy and severe intraventricular hemorrhage (Aucott et al., 2010). In the long term, a number of clinical evidence showed that abnormal HPA axis activities resulting from preterm birth are long-lasting. However, current findings on some aspects are inconsistent. For example, some showed that children born extremely preterm presented a higher cortisol level in the morning and higher cortisol urinary excretion when compared with peers born full-term (Buske-Kirschbaum et al., 2007; Gohlke et al., 2015; Kaseva et al., 2014; Urfer et al., 2021). On the other hand, some demonstrated that preterm-born children had a blunted morning cortisol level and lower urinary excretion (Landmann et al., 2021; Watterberg et al., 2019). In addition, one study found a higher basal cortisol level in young adults born preterm than peers born full term, while another showed a similar level (Kaseva et al., 2014; Szathmári et al., 2001). These short-term and long-term results indicate that dynamic programming of the HPA axis by preterm birth is possibly related to multiple perinatal factors, such as gestational age, perinatal illness, and medical treatment. Further studies are needed to investigate the underlying mechanisms of dysregulated HPA axis. It is likely to be associated with epigenetic modifications of cortisol receptors in the long term (reviewed in (Buschdorf et al., 2015)). It is also noted that inflammation plays a vital role in HPA axis programming. Very preterm infants exposed to prenatal inflammation (chorioamnionitis with funisitis) differ dramatically in terms of cortisol patterns from those without a history of prenatal inflammation at 18 months corrected age (Gover et al., 2013). Inflammation-induced cytokines (*i.e.* IL1β, IL6) can activate the HPA axis, promoting cortisol secretion. Excess cortisol in turn regulates microglia to release more pro-inflammatory cytokines and chemokines (Cheiran Pereira et al., 2022). Given the fact that infants with EoP have a history of both preterm birth and neuroinflammation as perinatal stressors, it is very likely for them to develop long-lasting HPA axis dysregulation.

Due to the fact that prenatal corticosteroids can significantly reduce the risk of perinatal death and respiratory distress syndrome, the most common clinical scenario is to administer one course of corticosteroids to women with anticipated preterm birth between 24 and 34 gestational weeks (Norman et al., 2021; Roberts et al., 2017). Thus, it is worth exploring whether the standard dose of exogenous corticosteroids could affect long-term metabolism through HPA axis programming. Although numerous animal studies showed that in utero exposure to dexamethasone led to impaired glucose metabolism and insulin resistance, current clinical evidence is insufficient and uncompelling to prove the long-term adverse effects of one-course corticosteroids on metabolism in children/adults born preterm (Dai et al., 2022; Ferreira et al., 2021). Firstly, compared with unexposed peers, children or adults who were exposed to prenatal corticosteroids did not show significantly a different cortisol level, indicating possibly undisturbed HPA axis activities (Dalziel et al., 2005a; Rakers et al., 2022; Winchester et al., 2016). Secondly, adults exposed to prenatal corticosteroids did not show impaired glucose

metabolism and insulin resistance (Dalziel et al., 2005a, 2005b; Finken et al., 2008). However, a study showed a functional reduction of pancreatic β cells (Kelly et al., 2012). It requires future human studies to focus on the secretion and action of insulin in children/adults born preterm at different gestational ages.

6. Conclusion

As neonatal medical care advances dramatically, preterm survivors with complications have become more common. It requires further studies on the long-term outcomes and underlying mechanisms. EoP is usually associated with neuroinflammation and/or systemic inflammation in preterm infants at different gestational ages and abnormal neurodevelopment in children/adolescents. In this review, we propose that EoP as one of the pro-inflammatory events predisposes neonates to metabolic diseases later in life regarding hypothalamic programming. The direct link between preterm birth and metabolic diseases has been established by numerous clinical evidence. Inflammation in EoP can lead to persistent functional and structural consequences due to vulnerability and plasticity in the developing brain. Thus, the synergic effects of preterm birth and neuroinflammation in EoP are likely to promote the development of metabolic diseases.

Here, we discuss the possible underlying mechanisms focusing on the developmental programming of the hypothalamus. Appetite-satiety control system and HPA axis are the most critical CNS and peripheral metabolism connections. On the one hand, EoP-induced neuroinflammation is mediated by reactive astrocytes and microglia partially through pro-inflammatory signaling. We hypothesize that it can dysregulate energy expenditure and food intake, sharing similar mechanisms with diet-induced obesity. On the other hand, preterm birth and/or prenatal inflammation are related to long-lasting abnormal HPA axis activities, leading to impaired glucose metabolism and insulin resistance.

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CRediT authorship contribution statement

Sihao Diao: Conceptualization, Writing – original draft, Writing – review & editing. **Chao Chen:** Conceptualization, Writing – original draft, Writing – review & editing. **Alexandre Benani:** Writing – original draft, Writing – review & editing. **Christophe Magnan:** Writing – original draft, Writing – review & editing. **Juliette Van Steenwinckel:** Writing – original draft, Writing – review & editing. **Pierre Gressens:** Writing – original draft, Writing – review & editing. **Céline Cruciani-Guglielmacci:** Writing – original draft, Writing – review & editing. **Alice Jacquens:** Conceptualization, Writing – original draft, Writing – review & editing. **Cindy Bokobza:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

There are no conflict of interest among all authors."

Data availability

No data was used for the research described in the article.

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