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Diet, behaviour and immunity across the lifespan

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Abstract

It is increasingly appreciated that perinatal events can set an organism on a life-long trajectory for either health or disease, resilience or risk. One early life variable that has proven critical for optimal development is the nutritional environment in which the organism develops. Extensive research has documented the effects of both undernutrition and overnutrition, with strong links evident for an increased risk for obesity and metabolic disorders, as well as adverse mental health outcomes. Recent work has highlighted a critical role of the immune system, in linking diet with long term health and behavioral outcomes. The present review will summarize the recent literature regarding the interactions of diet, immunity, and behavior.

Keywords

diet; nutrition; immune; inflammation; microglia; cytokine; IL-18; obesity; calorie restriction; lipopolysaccharide

1. Introduction

The incidence of obesity has now reached epidemic proportions within our society, with upwards of 50 percent of the population classified as overweight or obese in many developed countries (Colagiuri *et al.*, 2010; Ogden *et al.*, 2014). Dietary factors clearly play a significant role in contributing to this phenomenon. Obesity is also characterized by systemic and central inflammation that causes and contributes to excess fat deposition (De

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Souza *et al.*, 2005; Gregor & Hotamisligil, 2011; Spencer, 2013a). This inflammatory profile leaves the individual highly susceptible to disease, particularly to those relevant to immune dysfunction, including diabetes, cancers, mood disorders, vascular dysfunction, and susceptibility to infection (Haslam & James, 2005; Noria & Grantcharov, 2013).

The developmental origins of health and disease (DOHAD) hypothesis suggests there are certain 'critical windows' throughout early life when aspects of physiology, including brain development, are particularly vulnerable to environmental influences. *In utero* development and early postnatal life are two of these. At these times, the nutritional environment can alter the ability of an organism to integrate metabolic and feeding information, thus predisposing the organism to excess weight gain long-term. Outside these critical windows, metabolic and feeding pathways are potentially less plastic, but can still be shaped by dietary influences. For instance, medium to long-term 'dieting' (calorie restriction) in adult life can improve health and lifespan, in part by altering the hypothalamic inflammatory milieu. This central immune profile is important in regulating hypothalamic pathways involved in feeding, and life-long alterations in cytokine balance can greatly influence how one processes nutritional information. Diet, and the associated changes in the immune profile are not only critical in programming metabolic and feeding-related information, but have significant influence extending beyond the hypothalamus and into brain regions governing executive function. As such, our diet can be incredibly important in establishing several aspects of our behavioral and immune profile across our lifespan (Figure 1). In this review we will address these aspects of the importance of diet throughout life.

2. Prenatal dietary programming of behavior and immunity across the lifespan

Nutrition during gestation can have lifelong impacts on an individual's health and behavior. In this period of embryonic and fetal development the mother's nutrition, particularly as it relates to her body weight and metabolism, appears to be absolutely critical to the later life health of her offspring.

This concept was first appreciated when epidemiological studies examined the long-term health outcomes of individuals who were *in utero* during the Dutch Hunger Winter (1944–1945). The offspring of these undernourished mothers had low birth weight and impaired glucose tolerance later in life compared to individuals born in flanking years (Ravelli *et al.*, 1998). These observations inspired the concept that an individual's risk of disease across their lifespan could be shaped by events that occurred much earlier in their lives; indeed during their time in the womb (Barker, 2004). Interestingly, the timing of exposure to famine within the gestation period is also critically important. Thus, people exposed to famine in early gestation in the Dutch Hunger Winter were at greater risk of developing coronary heart disease and obesity in later life, whereas those exposed to famine in mid and late gestation were not similarly affected (Ravelli *et al.*, 1976; Ravelli *et al.*, 1999; Roseboom *et al.*, 2000b). Moreover, impaired glucose tolerance in offspring appears more likely to result from undernutrition in late than early gestation (Ravelli *et al.*, 1998). Within the Barker study, and a subsequent study that examined the Chinese Famine in the late 1950s-60s, was

the further observation that offspring who were most affected were those who, as their lives progressed, consumed a relatively high-fat Western diet and became obese (Ravelli *et al.*, 1998; Li *et al.*, 2010). Thus, maternal undernutrition elevates the risk of low birth weight babies, which in turn elevates the risk for obesity and diabetes later in life (Barker, 2006; Gluckman *et al.*, 2008). In addition to elevating the risk for obesity, exposure to famine *in utero* has also been linked to an increased risk for adverse mental health outcomes, including schizophrenia (Susser & Lin, 1992; Clair *et al.*, 2005), addiction (Franzek *et al.*, 2008), and affective disorders (Brown *et al.*, 1995).

With the recent increase in obesity across the Western world, much focus has now shifted to understanding the long-term health outcomes of individuals whose mothers were obese prior to or during pregnancy. Curiously, the epidemiological data paint a similar picture to undernutrition. Individuals whose mothers were obese during pregnancy show rapid postnatal growth, and a significantly higher risk for later life obesity, and "the metabolic syndrome" (Law *et al.*, 1992; Gale *et al.*, 2007; Armitage *et al.*, 2008; Crozier *et al.*, 2010; Tamashiro & Moran, 2010; Alfaradhi & Ozanne, 2011; Ornoy, 2011). Further, they also show increased risk for a constellation of behavioral and mental health problems, including autism, attention deficit/hyperactivity disorder, developmental delay, anxiety, and depression (Herva *et al.*, 2008; Rodriguez, 2010; Van Lieshout & Boyle, 2011a; Van Lieshout & Boyle, 2011b; Colman *et al.*, 2012; Halmoy *et al.*, 2012; Krakowiak *et al.*, 2012; Moore *et al.*, 2012; Wojcik *et al.*, 2013), risks which are also shared between those that experience undernutrition *in utero* (Grissom & Reyes, 2012). Finally, maternal dietary micronutrients and exposure to toxicants independent of body weight have both been reported to alter offspring metabolic and neurobehavioral disease risk. For example, in Indian populations it was found that low maternal vitamin B_{12} increased offspring risk for insulin resistance, and exposure *in utero* to the fungicide tibutyltin elevates offspring adiposity (Heindel, 2003; Yajnik *et al.*, 2008; Heindel & Schug, 2013).

Although nutrition during gestation and nutrition after birth are key contributors to neurobehavioral disease risk across the lifespan, the mechanisms that link these factors, either alone or together, to health risks and outcomes remain poorly understood. Animal models, typically rodent, sheep, or non-human primate (NHP), have been invaluable in shedding light on the cellular and molecular details occurring behind the scenes. In these models, research has traditionally focused on defining the altered function of offspring peripheral organs involved in metabolism, such as the pancreas, liver, adipose depots, and skeletal muscle whose function is impaired in obesity and the metabolic syndrome. However, since body weight and metabolic function are coordinately regulated by the brain (Stanley & Leibowitz, 1984; Fan *et al.*, 1997; Cowley *et al.*, 1999; Horvath *et al.*, 1999; Cone *et al.*, 2001; Cowley *et al.*, 2001; Elmquist *et al.*, 2005), and since maternal nutrition during pregnancy programs an assortment of offspring neurological abnormalities, studies examining changes in the offspring brain have become increasingly prevalent.

2.1 Animal models of maternal undernutrition during pregnancy

Two common models of undernutrition have been used: global undernutrition ranging from 20–70% of normal calories; and protein restriction, typically ~8% instead of 20% in normal

diet. Both produce intrauterine growth restriction (IUGR) and low birth weight in animal models. After birth, IUGR leads to rapid postnatal catch-up growth, an accompanying increased risk of metabolic pathologies later in life (Cottrell, 2007; Fernandez-Twinn, 2006), and a significantly reduced lifespan (Jennings *et al.*, 1999; Ozanne & Hales, 2004). It is now becoming apparent that limiting this catch-up growth / very rapid postnatal weight gain can eliminate the risk of obesity developing. Thus, IUGR rodents do not develop obesity if their food is also restricted during the suckling period, but do become obese if allowed *ad libitum* food during this time (Desai *et al.*, 2005; Berleze *et al.*, 2009). In humans, data from the 1941–44 Siege of Leningrad Famine also support the notion of the importance of catch-up growth. Unlike in the Dutch Famine, the Leningrad Siege saw victims having poor nutrition for long periods before and after the famine, which likely meant there was no opportunity for significant catch-up growth (Leon *et al.*, 1997; Roseboom *et al.*, 2000a). Consequently, there was no association between perinatal malnutrition and adult obesity in this cohort (Stanner *et al.*, 1997). The dilemma for physicians is that catch-up growth in IUGR babies can be essential for appropriate brain and lung development, so strategies to limit accelerated early postnatal weight gain need to be approached with caution (Brandt *et al.*, 2003).

The very early postnatal responses of the offspring to maternal undernutrition are signaled in the neonatal period by a premature, and kinetically altered postnatal leptin surge (Yura *et al.*, 2005). Hypothalamic development has been shown to be vulnerable to maternal malnutrition, with offspring demonstrating alterations in hypothalamic metabolism and plasticity (Alexandre-Gouabau *et al.*, 2012), as well as extensive alterations in neuropeptide expression (Núñez *et al.*, 2008; Remmers *et al.*, 2008; Coupé *et al.*, 2009). Thereafter, the later-life risks are underpinned by persistent changes in the function of peripheral metabolic tissues in adulthood. For example, liver function appears to be biased toward conservation of energy stores, including altered gluconeogenesis, greater glycogen content, and enhanced glucose storage (Burns *et al.*, 1997; Gosby *et al.*, 2003; Lie *et al.*, 2014). Adipocyte morphology may be altered, response to hormones disrupted, and expression of inflammatory markers and macrophage infiltration increased (Guan *et al.*, 2005; Ferland-McCollough *et al.*, 2012; Reynolds *et al.*, 2013b). Accompanying the inflammatory changes in adipose tissue, bone marrow macrophages appear hypersensitive to challenge, at least when presented *in vitro* with an acute inflammatory stimulus (lipopolysaccharide; LPS) (Reynolds *et al.*, 2013a), while circulating immune cells appear to respond in an opposing manner, with attenuated peripheral T-cell responses (Badr & Mohany, 2011) and decreased responses to LPS (Desai *et al.*, 2009). In the brain, for example, the development of hypothalamic neurons and their neural circuits in the postnatal period is disrupted (Delahaye *et al.*, 2008; Coupe *et al.*, 2010; Rocha *et al.*, 2014), markers of oxidative stress may be increased, and myelination defects stemming from disrupted oligodendrocyte differentiation have been observed (Reid *et al.*, 2012). Behaviorally, growth-restricted offspring have shown hyperactivity (Vucetic *et al.*, 2010b), circadian disruptions (Sutton *et al.*, 2010; Orozco-Solís *et al.*, 2011), altered sleep homeostasis (Shimizu *et al.*, 2013), and increased sensitivity to drugs of abuse (Shultz *et al.*, 1999; Valdomero *et al.*, 2007; Palmer *et al.*, 2008; Vucetic *et al.*, 2010b). For example, Shimizu et al showed that 50% dietary restriction from embryonic day (E)12 to birth leads to an enhancement of electroencephalogram (EEG) slow wave

activity (SWA) during non-rapid eye movement (NREM) sleep without changing the diurnal pattern or amounts of wakefulness, NREM, or rapid eye movement (REM) sleep. In addition, restricted mice also displayed an enhancement of EEG-SWA rebound after 6 hours sleep deprivation and a higher threshold for waking in the face of external stimuli (Shimizu *et al.*, 2013). Accompanying these behavioral changes, alterations in dopamine (Palmer *et al.*, 2008; Vucetic *et al.*, 2010b), glutamate (Palmer *et al.*, 2008), and catecholamine (Petry *et al.*, 2000) expression have been observed. Reductions in circulating levels of ACTH, adrenaline, and noradrenaline, but not leptin or testosterone have also been reported (Govic *et al.*, 2008; Levay *et al.*, 2008; Levay *et al.*, 2010a).

2.2 Animal models of maternal obesity during pregnancy

Animal models of maternal obesity typically use a high fat or high fat / high sugar ("cafeteria") diet to induce obesity prior to mating, although variations including high fat feeding at the time of mating, or high fat feeding in a particular window of gestation, have also been reported. The offspring of obese pregnancies from a variety of animal models, including rodent, sheep and NHP, show changes in peripheral metabolic tissues that are remarkably similar to those observed in the offspring from undernourished mothers. For example, among rats, neonates from obese pregnancies show an amplified and prolonged leptin surge accompanied by elevated leptin mRNA expression in abdominal white fat (Kirk *et al.*, 2009). In rat, mouse and sheep models, the offspring of obese mothers become hyperinsulinemic and hyperlipidemic, and show glucose intolerance, leptin resistance, increased adiposity (Ferezou-Viala *et al.*, 2007; Samuelsson *et al.*, 2008; Morris & Chen, 2009; Nivoit *et al.*, 2009; Long *et al.*, 2010), and disrupted insulin signaling in adipose tissue (Fernandez-Twinn *et al.*, 2014). In mouse and NHP models, altered liver function, including evidence of oxidative damage, altered mitochondrial function, and lipid accumulation with a propensity to develop non-alcoholic fatty liver disease have also been reported (Bruce *et al.*, 2009; McCurdy *et al.*, 2009; Alfaradhi *et al.*, 2014).

Maternal obesity can also have adverse consequences for offspring immune system functioning. Maternal obesity during pregnancy is a risk factor for offspring obesity and is associated with increased circulating high sensitivity C-reactive protein (hs-CRP) in offspring at 12 years of age (Leibowitz *et al.*, 2012). Consistent with preclinical findings, in a rat model of maternal obesity, exposure to a high fat diet during pregnancy increases basal and LPS-stimulated interleukin (IL)-1β concentrations in the hippocampus and increased LPS-stimulated IL-6 serum concentrations in adult offspring compared with controls (Bilbo & Tsang, 2010). Furthermore, exposure to maternal high fat diet increases basal and LPS-induced microglial activation in the hippocampi of neonatal and adult offspring compared with controls (Bilbo & Tsang, 2010).

Behaviorally, among rats and mice, offspring born to obese dams can exhibit hyperphagia (Samuelsson *et al.*, 2008; Nivoit *et al.*, 2009). This is likely to be driven by a combination of changes taking place in the regions of the brain that regulate body weight and homeostatic food intake, including the arcuate nucleus of the hypothalamus (ARC) and the paraventricular nucleus of the hypothalamus (PVN). Additionally, brain areas associated with food seeking and reward are known to be altered by maternal obesity and/or

consumption of a high fat diet. These changes include altered expression of appetite-regulating neuropeptides, altered proliferation of body weight-regulating neurons (Chang *et al.*; Chen *et al.*, 2009), ARC neuron leptin resistance, as judged by reduced phosphorylated signal transducer and activator of transcription 3 (pSTAT3) in response to exogenous leptin administration, and developmental alterations in the neural circuitry that regulates body weight (Bouret *et al.*, 2008; Kirk *et al.*, 2009; Sanders *et al.*, 2014a). In the reward pathways, altered gene expression in the opioid system (Grissom *et al.*, 2014), and changes in the mesolimbic dopamine pathways, including alterations in gene expression of DA-related genes (Vucetic *et al.*, 2010a), increased dopamine synthesis in the nucleus accumbens (NAc) and ventral tegmental area (VTA), and altered dopamine responsiveness in the NAc accompanied by reduced dopamine receptor D2 expression in the VTA (Naef *et al.*, 2008; Naef *et al.*, 2011). In the offspring hippocampus, abnormalities have been observed in neural circuit formation, neurogenesis and cell death both in the late gestation fetus and in the early postnatal period (Niculescu & Lupu, 2009; Tozuka *et al.*, 2009; Tozuka *et al.*, 2010).

Although relatively less studied compared to the effects of *in utero* growth restriction, the effects of maternal obesity or excessive gestational weight gain during pregnancy on the developing child have begun to be explored (Lieshout *et al.*, 2011). Epidemiological studies have found support for a link between maternal obesity and adverse neurobehavioral development, including cognitive delay (Casas *et al.*, 2013; Tanda *et al.*, 2013), and inattention and negative emotionality (Rodriguez, 2010), although negative findings have also been reported (Brion *et al.*, 2011). Maternal conditions, including diabetes, hypertension and/or obesity were also found to increase the risk for developmental delay and autism (Krakowiak *et al.*, 2012)..

In animal models, offspring from obese and/or high fat fed dams also exhibit behavioral changes that are consistent with the associations between maternal obesity and some aspects of offspring mental illness observed in humans. For example, in rat and mouse models, the offspring of obese mothers show defects in spatial learning in the Barnes maze test (Tozuka *et al.*, 2010), elevated anxiety (Bilbo & Tsang, 2010; Bland *et al.*, 2010; Can *et al.*, 2012; Sasaki *et al.*, 2014) and altered reward seeking behaviors (Naef *et al.*, 2008; Naef *et al.*, 2011), with an increased locomotor response to a D2/D3 agonist, and increased operant responding for fat, but not sugar, in rats born to dams fed a high fat diet during gestation (Naef *et al.*, 2011). Similarly, dams that were fed either a high fat diet or a highly palatable diet (high in carbohydrates) had offspring that demonstrated deficits in reversal learning, as well as decreased dopamine transporter (DAT) binding in the caudate, deficits that existed even in the absence of differences in body weight or serum glucose, insulin, or leptin (Wu *et al.*, 2013). In the postnatal period, hippocampal changes appear to be underpinned by increased oxidative stress and a deficiency in brain derived neurotrophic factor (BDNF) (Tozuka *et al.*, 2009; Tozuka *et al.*, 2010).

Although not comprehensive, the above summary demonstrates that substantial progress has been, and is being, made in defining the spectrum of changes that develop after birth when an individual has undergone gestation in an obese or undernourished mother. What remains to be discovered is what happens during gestation: what molecular factors are important, and

how do they act on the developing organism to affect the changes that increase disease risk much later in life?

2.3 Inflammation during pregnancy - A causative role?

Although many factors are involved in programming an individual's disease risk in later life, the immune system stands out for its importance in contributing to obesity and its sequelae because it has a critical and highly regulated role at the fetal-maternal interface during normal pregnancy; for example, ensuring appropriate trophoblast invasion, and tolerance of the mother's immune system to the developing, immunologically distinct, fetus (Lin *et al.*, 1993; Arck & Hecher, 2013). Thus, the focus here will be on factors produced by the immune system that may have the ability to modulate the course of development and/or developmental programming. Cells of the immune system produce a vast number of molecules whose purpose is mainly to modulate immune system function, be it local inflammation following tissue injury or the more systemic, whole body, response to foreign substances. These regulatory molecules, called cytokines, fall into two broad classes: pro-inflammatory and anti-inflammatory. In the classic immune response the two antagonize one another in a carefully orchestrated manner in order to precisely regulate the vigor and duration of the immune response. These interactions are highly complex; so much so that some cytokines may have both pro- and anti-inflammatory actions in distinct situations. In addition, cytokines act via receptors that are present on many cell types that are classically considered outside the immune system, including neurons, hepatocytes, cardiac and skeletal muscle (Fahmi *et al.*, 2013; Kammoun *et al.*, 2013; Sanders *et al.*, 2014b). Moreover, cytokine:receptor interactions are able to initiate signaling pathways, such as kinase cascades, that can regulate biochemical processes and changes in cellular physiology in a variety of cell types. Not surprisingly, they are beginning to surface as candidates that when aberrantly present, could disrupt developmental processes before birth.

2.3.1 Maternal inflammatory cytokines—Low grade, chronic activation of the immune system and the elevation of inflammation-modulating cytokines are hallmarks of both undernourished and obese adults (Hotamisligil *et al.*, 1993; Fried *et al.*, 1998; Das, 2001; Sartipy & Loskutoff, 2003; Weisberg *et al.*, 2003; Khaodhiar *et al.*, 2004; De Souza *et al.*, 2005; Bastard *et al.*, 2006; Wisse *et al.*, 2007). This has led to the idea that in the pregnant state, maternal body weight-associated inflammatory factors from the mother's circulation may impinge upon the embryo, fetus or both, and act upon responsive cells. A variety of cytokines, including, IL-1β, IL-6, monocyte chemoattractant protein 1 (MCP1), interferon gamma (IFNγ), IL-10, and tumor necrosis factor (TNF) have been observed to be elevated in association with obese pregnancy in both humans and rodents (Catalano *et al.*, 2009; Madan *et al.*, 2009; Roberts *et al.*, 2011; Kepczynska, 2013). Studies that have in turn examined the cytokine profile in the fetal circulation in maternal obesity have identified elevated IL-6, TNF, chemokine (C-C motif) ligand 2, IL-17A, and IFNγ (Desai *et al.*, 2013; Kim *et al.*, 2014). Although the majority of these cytokines are pro-inflammatory, one of them (IL-10) is anti-inflammatory, and another (IFNγ) is considered regulatory (i.e., neither pro- nor anti-inflammatory). This raises the question of whether there might be opposing actions among the cytokines. This has yet to be addressed in detail, but it seems reasonable

to suspect that a balance of biochemical activity would result from the combined actions of a panel of cytokines acting on particular tissues at particular developmental times.

In keeping with the notion that cytokines in the maternal circulation may affect the fetus, injection of isolated cytokines into pregnant dams appears sufficient to alter offspring development. For example, IL-6 or TNF injected into pregnant rat dams in mid-pregnancy (gestational days 8 (GD 8), 10 and 12) produced offspring with elevated body weight, adiposity, and decreased insulin sensitivity at birth (Dahlgren *et al.*, 2001). Injection of IL-6 on these days or during late pregnancy (GD 16, 18, 20) additionally produced neuronal loss in the hippocampus, impaired learning manifested as longer escape latencies in the Morris Water Maze, and hypertension (Samuelsson *et al.*, 2004; Samuelsson *et al.*, 2006a; Samuelsson *et al.*, 2006b). Further, administration of IL-6 into pregnant mice on GD12.5 caused deficits in pre-pulse inhibition in the offspring (Smith *et al.*, 2007b). Also, injection of IL-1β in late pregnancy (GD17–21) resulted in offspring with altered stress response and impaired learning (Gotz *et al.*, 1993).

The transfer of cytokines in the maternal circulation to the fetus *in vivo* has been demonstrated directly using radiolabeled IL-6 (Dahlgren *et al.*, 2006). For IL-1α, IL-1β, and TNF, *in vitro* assays of placental permeability also suggest that transfer can occur *in vivo* (Kent *et al.*, 1994). Importantly, only a fraction of the cytokine present in the maternal circulation appears to reach the fetus (Kent *et al.*, 1994), and whether these levels are sufficient to produce cellular and molecular alterations in fetal tissues *in vivo* is not clear. This is in contrast to reports that the human term placenta does not appear to be permeable to IL-1β, TNF, or IL-6 (Aaltonen *et al.*, 2005). This discrepancy may be explained by differences in preparations, species, or developmental timing, and a clear picture of maternal cytokine transfer to the embryo or fetus *in vivo* has not yet come into focus.

2.3.2 Placental inflammatory cytokines—In addition to maternal production of cytokines, the placenta also produces substantial cytokines in obese pregnancies across species, including humans (Hauguel-de Mouzon & Guerre-Millo, 2006; Radaelli *et al.*, 2006; Challier *et al.*, 2008; Zhu *et al.*, 2010a; Heerwagen *et al.*, 2013; Kim *et al.*, 2014). Based on these and similar observations, it has also been suggested that the placenta may amplify, dampen or otherwise transform maternal inflammation, so as to gate the inflammatory environment that the fetus is exposed to (Zaretsky *et al.*, 2004; Aaltonen *et al.*, 2005; Dahlgren *et al.*, 2006; Hauguel-de Mouzon & Guerre-Millo, 2006; Challier *et al.*, 2008; Zhu *et al.*, 2010b). In keeping with this, a recent study reported that inflammatory markers in the fetal circulation do not change significantly until late gestation in the mouse, despite elevated maternal inflammation much earlier (Kim *et al.*, 2014). This is consistent with the idea that the placenta is able to protect the developing fetus from elevated maternal inflammation, at least up until late gestation (Lenz, 1997; Houser, 2012).

2.3.3 Fetal inflammatory cytokines—Finally, it is also likely that the fetus itself may be the source of its own inflammatory cytokines that may exert pathological effects on its own development. The literature to date has focused mainly on postnatal offspring inflammatory responses, however, several tissues have been described to show altered inflammatory cytokine profiles in fetuses developing in obese mothers. For example, in a

sheep model, fetal large intestine expressed mRNA for a variety of cytokines and inflammation-mediating receptors (IL1α, IL-1β, TNF, IL-6, toll-like receptor (TLR)2, TLR4, TGF, IL-17) (Yan *et al.*, 2011). In the mouse, fetal adipose tissue showed elevated CCR2 and TNF mRNA expression (Murabayashi *et al.*, 2013). In the NHP, fetal liver cytokines have not been examined, however, triglyceride levels are increased, which may stimulate production of inflammatory mediators (McCurdy *et al.*, 2009).

Upon reaching the embryo or fetus, irrespective of route, it is imagined that inflammatory factors may either change the course of tissue development or alter the regulation of tissue-specific gene expression that is necessary for normal adult function later in life; in either case ultimately impairing tissue function to work less efficiently later in life. Studies in this domain are just beginning to emerge. For example, we have shown recently, that IL-6, which is elevated in the maternal and fetal circulation, is able to alter the prenatal formation of body weight-regulating neural circuits in the ARC (Sanders *et al.*, 2014a). However, the full impact of aberrant exposure to inflammatory mediators associated with maternal nutritional status on developing tissues, particularly the brain, remains a mostly open question.

In considering how cytokines or other factors in the peripheral fetal circulation might affect the brain, one additional consideration is whether cytokines actually reach the fetal brain to effect cellular and molecular changes that increase offspring risk for behavioral abnormalities. In the adult, factors such as IL-6 and leptin, when present in the peripheral circulation, can impinge on ARC neurons via specific transport across the blood brain barrier (BBB; Banks, 2006; Pohl *et al.*, 2013; Koch *et al.*, 2014). There is some controversy regarding the exact time of maturation of the BBB during embryonic development (Engelhardt & Liebner, 2014). Thus, the timing of BBB maturation and adult-like function will determine when during gestation specific factors in the fetal circulation could gain access to the fetal brain. At early times during gestation when the BBB is not yet fully functional, blood-borne factors may be able to gain access via free diffusion or some other process that is not present in the mature BBB. Tagging of peripheral factors, as has been done with leptin in the adult brain (Vauthier *et al.*, 2013; Balland, 2014), may be one approach to resolving this important question (for example, see Banks *et al.*, 2004).

Finally, there is the possibility that inflammatory mediators may be aberrantly produced by brain-resident cells in maternal under or overnutrition. In the NHP model of maternal obesity, the fetal hypothalamus showed increased expression of IL-1 and C-C chemokine signaling family genes, as well as an increase in activated microglia (Grayson *et al.*, 2010). Although the presence of inflammatory cells within the brain may at first glance seem to obviate the need to get cytokines across the BBB, there is still the question of how these brain resident cells receive their information regarding maternal nutritional status. Microglia develop from the yolk sac and enter the brain beginning on GD10 in the mouse (Takahashi *et al.*, 1989). During this time they could be exposed to cytokines of maternal, placental or fetal origin, making it likely that they enter the brain already primed or activated. Unfortunately, the early stages of microglia development *in utero* have remained largely elusive, and how early circulating factors may influence microglial function later in life are unknown.

Although this review has so far been restricted to inflammatory factors, in reality any diffusible substance whose expression or presence in fetal tissues is altered by maternal nutrition would be a candidate for mediating the changes associated with disease programming. Other factors which are gaining ground for their importance in disease risk programming by maternal nutritional status are fatty acids (de Vries *et al.*, 2014; Loomans *et al.*, 2014), which are able to signal through TLRs to initiate an inflammatory response (Hwang & Rhee, 1999; Brikos & O'Neill, 2008; Yin *et al.*, 2014), and growth factors such as BDNF (Tozuka *et al.*, 2009; Tozuka *et al.*, 2010), epidermal growth factor (Serrero *et al.*, 1993), and fibroblast growth factors (Hutley *et al.*, 2004; Huang *et al.*, 2007). Recently, the role of the gut microbiome in health and disease has received significant attention (Palma *et al.*, 2014), and in regard to early life programming, parental consumption of a Western diet was shown to alter concurrently the offspring immunity and gut microbiome (Myles *et al.*, 2013). In a NHP model, maternal high fat diet was also shown to alter the offspring gut microbiome, independent of offspring obesity (Ma *et al.*, 2014).

3. Postnatal dietary programming of behavior and immunity across the lifespan

3.1. Neonatal nutrition programs physiology long-term

As discussed, prenatal life is clearly a time of significant vulnerability to long-term programming of health and disease. A second such critical window of vulnerability occurs in the days to weeks after birth (Spencer *et al.*, 2006; Spencer & Tilbrook, 2011; Spencer, 2012). As such, the neonatal nutritional environment can have substantial long-term programming effects on an individual's feeding behavior, satiety signaling, and metabolism, and can play an important role in susceptibility to obesity (Spencer, 2013a; Spencer, 2013b). This neonatal nutritional environment also influences the development of obesity-associated disorders, including those related to a dysfunctional immune system, such as diabetes, cancers, and susceptibility to infection (Spencer, 2013a; Spencer, 2013b).

3.2. Neonatal nutrition affects metabolism and susceptibility to obesity long-term

In humans, childhood overweight and obesity are considered substantial risk factors for the development of obesity in later life (Ong *et al.*, 2000; Stettler *et al.*, 2005). Incredibly, one study has found for every 100 g of weight a baby puts on in the seven days after birth, the likelihood of that baby becoming an obese adult increases by 28 percent (Stettler *et al.*, 2005). Early work has also outlined that the likelihood of becoming an obese adult increases from 10 percent to approximately 50 percent if the subject was classified obese as a child, with this risk magnifying with degree of childhood obesity (Whitaker *et al.*, 1997). While a portion of the risk associated with neonatal nutrition and neonatal obesity may be linked to genetic and later environmental factors, this does not seem to fully explain the effects. For instance, genetic factors may predispose a child to both metabolic disturbances and poor nutritional choices throughout life. However, body mass index (BMI) has to date been identified as having anything from a 40 to a 70 percent genetic component, with only around two percent of obesity-susceptible genetic loci identified, indicating other factors are likely to contribute (Loos, 2009). Likewise, poor nutritional choices made by parents on a child's

behalf early on may instill a culture or habit of poor eating practices that are continued throughout life (Colapinto *et al.*, 2007). However, this potential variable is not included in studies using animal models of neonatal overfeeding, where early neonatal nutrition is still able to program metabolic phenotype long-term.

3.3. Neonatal nutritional programming of neuroimmune function

One such animal model of neonatal overfeeding, suckling rats in small litters, reveals the neonatal nutritional environment has substantial impact on long-term metabolic function and weight gain. Thus, pups suckled in small litters, where they have greater access to the dam's milk and receive milk that is higher in fat (Fiorotto *et al.*, 1991), have accelerated growth and development, weigh more early on than their control-litter counterparts, and maintain excessive weights and fat deposition into adulthood (Clarke *et al.*, 2012). These rats also have differences in metabolic function (Stefanidis & Spencer, 2012) and in such diverse physiological functions as stress responses (Spencer & Tilbrook, 2009), puberty onset (Smith & Spencer, 2012), bone structure (de Albuquerque Maia *et al.*, 2014), and wound healing (Sabol *et al.*, 2014). As is seen with adult-onset obesity (Pohl *et al.*, 2009; Clarke *et al.*, 2012), neonatally overfed rats also have exacerbated febrile and pro-inflammatory cytokine responses to a neuroimmune challenge (Clarke *et al.*, 2012).

In humans, obesity is linked to a dysregulated immune system, with systemic and central inflammation and an inability to appropriately respond to an infection. For instance, obese people are twice as likely to contract pneumonia as lean people are. They are up to six times as likely to develop post-surgical infections, and are more than twice as likely to die in intensive care from an infection-related complication (Falagas & Kompoti, 2006). Childhood obesity in particular is linked to disorders of the immune system, including autoimmune disorders such as asthma and atopy (Celedon & Kolls, 2014). Childhood obesity is also linked to increases in morbidity and mortality after hospitalization for acute illness or organ transplants, with increased incidence of infections playing a role (Bechard *et al.*, 2013). Probably contributing to this increased morbidity and mortality, obese people can have exacerbated neuroimmune responses to an immune challenge. For instance, obese diabetic patients undergoing laproscopic Roux-en-Y gastric bypass surgery have a significantly greater increase in pro- and anti-inflammatory cytokines IL-6 and IL-10 than lean patients do after a similar surgery (Lin & Gletsu-Miller, 2013). Similarly, circulating cytokine levels following hip surgery have been correlated with BMI, implying the immune system is primed to over-react to immune stimuli in obese people (Motaghedi *et al.*, 2013). Consistent with these findings in obese adult humans, neonatally overfed rats have exacerbated febrile and circulating pro-inflammatory cytokine responses to an immune challenge with bacterial endotoxin, LPS (Clarke *et al.*, 2012). They also have increased inguinal fat TLR4 expression, and increased inguinal fat phosphorylated inhibitory factor κB (IκB) (Clarke *et al.*, 2012).

Unlike adult-onset obesity in humans, or adult high fat diet in rodent models, however, neonatal overfeeding does not seem to affect sickness behavior responses to LPS to the same degree, including activity levels or anorexia (Clarke *et al.*, 2012). The reasons for this specificity of response are currently unknown. However, it may be that the pathways

regulating these aspects of sickness behavior remain intact in the neonatally overfed rats, while those affecting TLR4- and febrile-dependent responses are selectively affected. For instance, leptin plays a role in sickness-induced anorexia (Sachot *et al.*, 2004), and leptin levels are not different between neonatally overfed and control rats after LPS (Clarke *et al.*, 2012). However, the pro-inflammatory cytokine IL-1 is also known to play a critical role in mediating sickness-induced anorexia (Reyes & Sawchenko, 2002; Nadjar *et al.*, 2010), and plasma levels of IL-1 do differ in response to neonatal overfeeding, highlighting the complexity of these physiological responses.

Neonatal overfeeding in this model also does not affect febrile responses to a viral mimetic, polyinosinic:polycytidylic acid (poly I:C). Responses to poly i:c are similar in neonatally overfed and control rats, despite increased inguinal fat TLR3 expression in the former group (Clarke *et al.*, 2012). Immune responses to viruses in adult humans and rodents are affected by metabolic status, with obese adult people and mice being more likely to contract and die from influenza (Smith *et al.*, 2007a; Fuhrman *et al.*, 2011). Although data on the susceptibility to viral challenges in obese children are lacking (Esposito *et al.*, 2012), it may be that neonatal overfeeding programs up-regulation of TLR3, but not the associated cell-transport mechanisms that would traffic the viral ligand into the cell (Clarke *et al.*, 2012). The result is somewhat encouraging for those with early life obesity, at least in terms of their potential to combat a viral, if not a bacterial, infection.

The mechanism for the overactive immune response in those with obesity and the difference in how this is manifest in those with obesity programmed early in life remain to be determined. However, the exacerbated response to a bacterial immune challenge that occurs in neonatally overfed rats is likely to be due, at least in part, to changes in hypothalamic-pituitary-adrenal (HPA) axis function. The HPA axis is normally activated in response to an immune challenge and culminates in the release of glucocorticoids into circulation (Sapolsky *et al.*, 2000; Papadimitriou & Priftis, 2009). Glucocorticoids then act on immune cells to suppress nuclear factor κB (NFκB)-mediated transcription of pro- and anti-inflammatory cytokines, thus dampening further activation of the immune response (Cartmell *et al.*, 2003; Conti *et al.*, 2004; Galic *et al.*, 2009; Spencer, 2013a). Synthetic glucocorticoids are used therapeutically to suppress overactive immune function (Flammer & Rogatsky, 2011) and an underactive HPA axis, or glucocorticoid resistance, is linked to exacerbated immune responses (Silverman & Sternberg, 2012). This negative feedback effect of the HPA axis, when appropriately functional, allows the immune response to effectively combat the invading pathogen, but helps prevent it from over-activation and excessive sickness (Spencer, 2013a).

There is evidence HPA axis function is disturbed in neonatally overfed animals. Thus, females (but not males) have greater neuronal activation in the PVN, the apex of the HPA axis, in response to a psychological stress if they were raised in small litters (neonatally overfed) compared with those raised in control litters (Spencer & Tilbrook, 2009). Both male and female neonatally overfed rats also have significantly greater PVN neuronal activation after an immune challenge with LPS than control rats (Clarke *et al.*, 2012). Neonatally overfed rats also have a glucocorticoid response to LPS that is significantly slower than that of control rats (Clarke *et al.*, 2012). Thus, control rats have a peak plasma

glucocorticoid response to LPS at around 30 to 60 minutes that is resolved back to baseline levels by 90 minutes. In neonatally overfed rats, however, glucocorticoid levels continue to remain elevated at 90 minutes after LPS exposure (Clarke *et al.*, 2012). We hypothesize neonatally overfed rats have an enhanced febrile and cytokine profile in response to LPS at least partly because the HPA axis is slow to release immuno-suppressive levels of glucocorticoids. This response is also reflected in less negative feedback onto central steps of the HPA axis, hence enhanced PVN neuronal activation. These effects of neonatal nutrition on HPA axis function are supported by data from a recent study showing neonatally overfed rats have an accelerated HPA axis maturation, coupled with changes in HPA axis sensitivity to stress in adulthood and enhanced mesenteric adipose tissue glucocorticoid receptor (GR) mRNA expression (Boullu-Ciocca *et al.*, 2005). As such, rats made overweight by being suckled in small litters have substantial increases in basal circulating adrenocorticotropic hormone (ACTH) and corticosterone at postnatal days 14 and 21, as well as reduced PVN corticotropin-releasing hormone (CRH) mRNA and enhanced PVN GR mRNA early on (Boullu-Ciocca *et al.*, 2005).

3.4. Neonatal nutritional programming of central inflammation

It is likely that, additional to changes in the glucocorticoid response to LPS, neonatally overfed animals are also more susceptible to a bacterial immune challenge due to changes in their central inflammatory profile. It is increasingly apparent that obesity and high fat diet lead to central, as well as peripheral inflammation (Pickup & Crook, 1998; Weisberg *et al.*, 2003; Wellen & Hotamisligil, 2003; De Souza *et al.*, 2005; Zhang *et al.*, 2008; Milanski *et al.*, 2009; Posey *et al.*, 2009; Thaler *et al.*, 2012). Obesity in humans is associated with increases in indices of inflammation in the brain, including microgliosis (Thaler *et al.*, 2012). Similarly, rodent models have revealed increased pro-inflammatory gene expression and cytokine production in the hypothalamus, including the ARC, after a short period of high fat diet feeding (De Souza *et al.*, 2005; Zhang *et al.*, 2008; Thaler *et al.*, 2012). Recently, Thaler and colleagues demonstrated this high fat diet-induced central inflammation in rodents was linked to pronounced changes in the resident immune cells of the brain, microglia and astrocytes (Thaler *et al.*, 2012). Human brains also show microgliosis after sustained obesity (Thaler *et al.*, 2012). As little as three days after the onset of high fat feeding, mice and rats have increased numbers of cells immunopositive for the microglial-specific marker, ionized calcium-binding adapter molecule (Iba1) (Thaler *et al.*, 2012). At this time they also have an elevated expression profile of pro- and anti-inflammatory cytokines in the hypothalamus (Thaler *et al.*, 2012). This inflammatory profile is likely to reflect an initially protective effect of microglial activation and proliferation, since the inflammation normalizes by seven days only to reappear by three weeks if the high fat diet is continued (Thaler *et al.*, 2012). With such prolonged high fat diet exposure, the central inflammation is associated with neuronal injury markers and an attrition of pro-opiomelanocortin (POMC) neurons in the ARC (Thaler *et al.*, 2012). Other groups have shown this hypothalamic inflammation can lead to leptin and insulin resistance within the brain and thus directly contribute to impairments in satiety signaling and further obesity (De Souza *et al.*, 2005; Posey *et al.*, 2009). When a diet high in fat is continued long-term in rodent models (e.g., 14 to 20 weeks), central inflammation and damage to extra-hypothalamic regions can also ensue (Jeon *et al.*, 2012; Puig *et al.*, 2012). Thus, rats fed high

fat diet for 14–20 weeks have hippocampal (Jeon *et al.*, 2012) and frontal cortex (Pepping *et al.*, 2013) microgliosis and increased levels of hippocampal pro-inflammatory cytokines (Jeon *et al.*, 2012). This type of inflammatory profile is also associated with alterations in tasks of cognitive function. For instance, mice with indices of hippocampal inflammation perform less well in the Morris Water Maze and this can be rescued with the anti-inflammatory agent, resveratrol (Jeon *et al.*, 2012). This potential link between central inflammation in obesity and cognitive dysfunction has recently been extensively reviewed (Miller & Spencer, 2014).

Commencing an inappropriate diet in adulthood can thus facilitate disruption of feeding- and metabolic pathways, but there is increasing evidence that the early life programming period is equally if not more important in this regard. As discussed in Section 2, *in utero* exposure to excess cytokines can alter the brain's inflammatory milieu and disrupt axon growth and appropriate neuronal activity. The brain is also still vulnerable to this type of influence in the early postnatal period. For example, cytokines are present in breast milk (Garofalo, 2010), and have been shown to affect fat and lean mass accrual in humans (Fields & Demerath, 2012).

The early postnatal period, in the rodent, is one when the brain's microglia complete their maturation from being few and amoeboid in morphology at E14 to 18 to being fully mature with an adult-like ramified morphology by Postnatal day (P)14 (Bilbo & Schwarz, 2009). Any stimulus that interferes with this maturation process is likely to alter the central inflammatory profile throughout life and thus susceptibility to future challenges. Bilbo and colleagues have shown early life exposure to bacterial infection has the effect of maintaining microglia in an immature 'active' state so they are effectively primed to over-respond to future immune stimuli (Bland *et al.*, 2010). Additionally, the predominant polyunsaturated fatty acid (PUFA) in the typical Western diet is n-6, with a relative deficiency in n-3 PUFAs, and deficiencies in n-3 PUFAs have also been linked to adverse neurobehavioral outcomes. Recently it was reported that n-3 PUFA deficiency during pregnancy led to altered microglial morphology and increased expression of hippocampal proinflammatory cytokines (Madore *et al.*, 2014). Importantly, we have recently reported neonatal overfeeding also leads to hypothalamic microgliosis early on, and this persists into adulthood despite resumption of a normal diet at weaning. These effects are associated with changes in hypothalamic pro-inflammatory cytokine gene expression and exacerbated microglial responses to LPS. These findings suggest neonatal overfeeding can also sensitize hypothalamic microglia, contributing to basal central inflammation and the hypersensitive response to an immune challenge throughout life (Ziko *et al.*, 2014).

The *in utero* and early postnatal periods are clearly of critical importance in dietary programming of behavior and immunity throughout life. This period appears to extend into the juvenile age as well. Recently, it was reported that consumption of a HFD in juveniles, but not adults, resulted in alterations in hippocampal inflammation, as well as deficits in spatial memory (Boitard *et al.*, 2014). However, although feeding and immune pathways are somewhat less plastic outside these critical windows, they are certainly still potentially vulnerable to environmental and dietary influence.

4. Dietary influences on immune function in adulthood: Calorie restriction

As well as during the critical prenatal and perinatal periods, dietary influences during adulthood can have profound effects on immune functioning. For example, exposure to a calorie restricted diet during adulthood can alter a number of immune system processes. Calorie restriction (CR), which usually involves the reduction of daily food intake while maintaining dietary composition and avoiding malnutrition (Weindruch & Walford, 1988), is perhaps best known for extending mean and maximum lifespan in a number of species ranging from yeast to mammals (Weindruch *et al.*, 1986). For example, in a population of rhesus monkeys at the Wisconsin National Primate Research Center (WNPRC) an adult-onset 30% CR regimen improved age-related and all-cause survival rate and delayed the onset of age-related diseases (Colman *et al.*, 2009; Colman *et al.*, 2014). In contrast, however, among a population of rhesus monkeys at National Institute on Aging (NIA), old-onset or young-onset 30% CR has shown no differences in survival compared with controls (Mattison *et al.*, 2012). Interestingly, control NIA animals were provided regulated portions of food according to dietary standards rather than fed *ad libitum*, possibly indicating that they underwent a mild CR themselves. Indeed, control animals at NIA had a lower than average body weight when compared to a national database of healthy, captive non-human primates (Colman *et al.*, 2014). Therefore, the lack of CR-induced differences in survival rate in NIA monkeys may result from the control monkeys experiencing survival benefits following a mild-CR. Given the control monkeys at WNPRC were provided unlimited access to nutrient dense food, an alternative explanation for the contrasting findings could be that these monkeys are over eating, resulting in a higher number of age-related diseases in this group. Of note, an earlier longitudinal study at the University of Maryland demonstrated that CR monkeys had a 2.6 fold reduced risk of death, an increased median survival age, and reduced age-related pathologies compared with *ad libitum*-fed control monkeys (Bodkin *et al.*, 2003).

Aside from effects on longevity, CR has been shown to elicit many health promoting benefits, including delaying the onset of multiple age-related pathologies, attenuating the progression of neurodegeneration in animal models of Parkinson's disease (Maswood *et al.*, 2004), Alzheimer's disease (Halagappa *et al.*, 2007), and multiple sclerosis (Piccio *et al.*, 2008), delaying the process of age-related immunosenescence (Koubova & Guarente, 2007), and reducing the growth of cancerous tumors (Berrigan *et al.*, 2002). Furthermore, CR can improve learning and memory (Komatsu *et al.*, 2008; Grayson *et al.*, 2013), increase social behavior (Govic *et al.*, 2009), reduce anxiety-like behavior (Levay *et al.*, 2007) and can dose-dependently increase circulating corticosterone and decrease circulating testosterone concentrations (Levay *et al.*, 2010b). In this section we will focus on the effects of a CR diet on immune system function.

4.1 Calorie restriction and immune function

As the effectiveness of the immune system often declines with age (Murasko & Goonewardene, 1990) and age-related diseases often have immune components (Jolly, 2004), considerable research has focused on elucidating the effects of CR on immunity. CR has been demonstrated to delay the age-related decline in immune efficiency (Weindruch &

Walford, 1988) and can reduce the age-associated elevation in cytokines to levels comparable to that of young animals (Spaulding *et al.*, 1997; Muthukumar *et al.*, 2000). The majority of research has demonstrated that CR results in decreased (or unchanged) concentrations of pro-inflammatory mediators (e.g., Dong *et al.*, 1998; Matsuzaki *et al.*, 2001; MacDonald *et al.*, 2011), coupled with increased concentrations of anti-inflammatory mediators (e.g., MacDonald *et al.*, 2011; MacDonald *et al.*, 2014) both at basal levels and following immune stimulation. However, due to significant variability between studies, the effect of CR on the immune response is not entirely clear.

Several lines of evidence have demonstrated unchanged basal pro-inflammatory cytokine concentrations following a CR regimen (Conn *et al.*, 1995; Sun *et al.*, 2001; Fenton *et al.*, 2009; Crissey *et al.*, 2014). For example, in rats, an eight week, 30% CR did not alter the serum concentrations of IL-6 or TNF; interestingly however, 30% CR did reduce expression of IL-6 and TNF mRNA in retroperitoneal and periaortic adipose tissue, but not in subcutaneous or interscapular adipose tissue (Crissey *et al.*, 2014). In contrast, other studies, also in rats, have shown that CR reduces circulating basal levels of pro-inflammatory cytokines, including IL-1β, IL-6, and/or TNF (Dong *et al.*, 1998; Ugochukwu & Figgers, 2007), and/or enhances the basal concentration of anti-inflammatory cytokines, such as IL-10 and IL-4 in rats and mice (Ugochukwu & Figgers, 2007; Fenton *et al.*, 2009).

In contrast to the equivocal effects of CR on basal concentrations of cytokines, the majority of findings suggest that CR attenuates peripheral inflammation and enhances immune function following immune stimulation. For example, 25% CR improves phagocytic function of alveolar macrophages, evident by a CR-induced enhanced clearance of a bacterial infection (*Streptococcus zooepidemicus*) from the lungs (Dong *et al.*, 1998). Further, macrophages of CR rats show decreased expression of TNF and IL-6 mRNA and decreased nitric oxide synthesis compared with *ad libitum* fed rats following LPS (Dong *et al.*, 1998). In addition, 40% CR attenuates the LPS-induced increase in IL-1β, IL-6, and TNF, which is associated with reduced serum aspartate and alanine aminotransferase activities, indications of liver injury (Matsuzaki *et al.*, 2001), suggesting improved immune function. Consistent with this finding, a 40% CR regimen causes a reduction in LPS-induced IL-6 and NFκB activity in splenocytes (Bhattacharya *et al.*, 2006). Peritoneal macrophages isolated from 40% CR mice produce less IL-6 and IL-12, but not TNF, following LPS compared to *ad libitum* fed mice. Additionally, CR animals have lower LPS-induced expression of TNF, IL-6, and IL-12 mRNA than *ad libitum* fed mice (Sun *et al.*, 2001). Exposure to a 40% CR diet also reduces IL-1β concentration in peritoneal macrophages following LPS; though there is no effect on levels of TNF, IL-6, or the anti-inflammatory cytokine IL-10 (Vega *et al.*, 2004). These discrepant findings in two studies that utilized the same magnitude of CR (40%) and site of cytokine measurement (peritoneal macrophages) highlight the importance of considering methodological differences in the CR regimens. Differences in the duration of CR (five months in Sun et al., 2001; 15 months in Vega et al., 2004) and/or the length of exposure of the macrophages to LPS (24 hours in Sun et al., 2001; five hours in Vega et al., 2004) may explain the differences in CR-induced cytokine production. Of note, Vega and colleagues also demonstrated that an intermittent fasting (IF) regimen, where mice had access to food every other day, reduced IL-1β and TNF levels, increased IL-6 levels, but had no effect on IL-10 following LPS (Vega *et al.*, 2004).

Although IF regimens and CR are known to result in similar weight changes, approximately 70% of *ad libitum* controls for 3 weeks of an IF regimen (Chausse *et al.*, 2014) or 3 weeks of 50% CR regimen (Levay *et al.*, 2007), it is likely that these different dietary conditions result in subtle differences in the immune response.

Finally, recent work conducted by our research group found that 50% CR induced an anti-inflammatory bias both peripherally and centrally following immune stimulation (MacDonald *et al.*, 2011; MacDonald *et al.*, 2014). Specifically, CR reduced LPS-induced IL-6 production and increased corticosterone in serum (MacDonald *et al.*, 2014). In addition, CR animals did not demonstrate the expected rise in hypothalamic pro-inflammatory signalling (COX-2, membrane prostaglandin E synthase 1 (mPGES-1)) at two hours post-LPS, but instead demonstrated delayed expression at four hours following LPS administration. At four hours post-LPS, there was also significantly enhanced expression of anti-inflammatory mediators suppressor of cytokine signaling 3 (SOCS3), IL-10, IκBα in the hypothalamus of CR animals (MacDonald *et al.*, 2011).

4.2 Calorie restriction, fever, and sickness behavior

Limited research exists investigating the effects of CR on fever and sickness behavior following immune stimulation. The effects of food deprivation on fever and sickness however, have been investigated. Food deprivation is a very different dietary challenge to CR and IF regimens. Typical food deprivation paradigms involve the complete removal of food for a period of hours or days. Food deprivation of two days results in weight loss to approximately 82% of *ad libitum* fed controls (Inoue *et al.*, 2008). Longer periods of food deprivation result in greater weight loss (78% and 71% of *ad libitum* fed controls for four and six days of food deprivation respectively (Shido *et al.*, 1989). Previous research has shown, in various experimental animals, that food deprivation negatively affects their ability to physiologically produce a fever after exposure to a pyrogen (Kleitman & Satinoff, 1981; Shojoony, 1985; Shido *et al.*, 1989; Inoue *et al.*, 2008). In addition, food deprivation attenuates the anorexic response of rats in response to continuous infusion of IL-1 (Mrosovsky *et al.*, 1989).

Recently, we demonstrated that a 50% CR regimen for four weeks completely attenuated LPS-induced sickness behavior, including fever, anorexia, and behavioral depression in both mice (MacDonald *et al.*, 2011) and rats (MacDonald *et al.*, 2014). Interestingly, this phenomenon is dose-dependent; CR for either shorter durations or smaller magnitude results in partial attenuation of the fever and other aspects of sickness behavior (MacDonald et al., 2011 and 2014).As outlined above, the suppression of sickness behavior was likely controlled by a reduction in pro-inflammatory signalling, coupled with an increase in anti-inflammatory signalling in CR mice (MacDonald *et al.*, 2011; MacDonald *et al.*, 2014).

4.3 Calorie restriction and central inflammation

To our knowledge, research investigating the effects of CR on microglial activation is limited. Mice exposed to an IF regimen for three months had reduced accumulation of microglia in the hippocampus one week following an intrahippocampal kainite injection designed to induce hippocampal damage as a consequence of excitotoxic seizure activity

(Lee, Auyeung, & Mattson, 2003). Similarly, rats subjected to three months of 50% CR demonstrate a reduction in microglial activation, TNF expression, and neuronal cell death following cortical injury (Loncarevic-Vasiljkovic *et al.*, 2012). Microglial cells surrounding the lesion site displayed predominantly reactive, amoeboid morphology in *ad libitum* fed rats compared with mainly ramified cells in CR rats, suggesting morphological differences between dietary groups (Loncarevic-Vasiljkovic *et al.*, 2012). Furthermore, a chronic CR regimen for 19 months suppresses the age-related increases in microglial activation to levels similar to that of young mice in the corpus callosum, basal ganglia, and subregions of the dentate gyrus (Morgan *et al.*, 1999). Finally, we have recently demonstrated that CR attenuates LPS-induced microglial activation in a subset of hypothalamic regions including the ARC and ventromedial hypothalamic nucleus (VMH) as well as the subfornical organ (Radler *et al.*, 2014).

5. Cytokines and Energy Homeostasis

Prenatal and perinatal programming as well as dietary changes during adulthood can alter the inflammatory milieu, which can have consequences for the maintenance of energy and nutrient homeostasis throughout life. Indeed, the clinical observation that sickness is often associated with anorexia, loss of appetite, or even cachexia, was historically the main evidence that molecules of the immune system may be able to influence appetite and energy homeostasis. Three cytokines have been recognized as main modulators of these actions and remain to date the most investigated: IL-1β, IL-6 and TNF. These three cytokines mediate several of the symptoms associated with sickness including sleepiness, malaise, fever, and loss of appetite (Dantzer, 2001; Kelley *et al.*, 2003). Indeed, it was generally believed that the appetite-suppressing effects of exogenous IL-1, IL-6, and TNF are inevitably linked to fever and malaise. However, recent data suggest a physiologic negative feedback role for these cytokines in energy homeostasis to curb fat accrual in the same manner as leptin. For example, IL-1β and IL-6 are hypersecreted from activated macrophages in white adipose tissue, and mice that lack the IL-1 receptor, IL-1/IL-6, or IL-1 become obese by 5–6 months of age (Wallenius *et al.*, 2002; Chida *et al.*, 2006; Garcia *et al.*, 2006). Conversely, although leptin historically has been primarily characterized as an adipocyte hormone that regulates energy homeostasis, data clearly indicate sickness/inflammatory-like functions of leptin (Lord, 2006). For example, inflammatory stimuli, such as LPS, induce leptin expression, and exogenous leptin can induce fever via induction of IL-1 (Luheshi *et al.*, 1999). Thus, the functional boundaries between “sickness” cytokines and “energy homeostasis” regulating cytokines have been blurred. Perhaps it is not surprising that components of the adaptive “sick syndrome” response to infection, often involving heat production and reduced food intake, may have been co-opted to also subserve energy balance.

Although some of the mediators have been identified, the mechanisms by which inflammation can affect nutrient homeostasis remain poorly understood. In this section, we review the evidence for the possible effects of maternal, placental or fetal inflammation in contributing to the programming of energy homeostasis. The sites of the anorexigenic action of pro-inflammatory cytokines also remain to be conclusively demonstrated. Cytokines are relatively easy to measure and are typically highly inducible, two features that makes them an attractive subject of investigation. However, they are also redundant, do not readily cross

the BBB, and often regulate each other's production making it difficult to determine the hierarchical order of action and whether these molecules can act centrally to modulate hypothalamic functions. Finally, the cytokine-mediated regulation of nutrient homeostasis appears to be finely regulated and the experimental evidence collected so far is not always easy to reconcile. For instance, while IL-1β, IL-6, TNF, as well as IL-18, are recognized to have anorexigenic effects, obesity is associated with a low grade, chronic inflammation characterized by the elevated level of pro-inflammatory cytokines. At present this is viewed to be similar to what is observed for the adipokine leptin as an ultimately failed attempt to maintain homeostasis and an acquired resistance state (Lago *et al.*, 2007). This attempt was shown to be at least in part mediated by the ability of cytokines whose levels increase with obesity to oppose positive energy balance via endocrine or vagally-mediated negative feedback to the mediobasal hypothalamus and caudal hindbrain (Plata-Salamán, 2001; Wong & Pinkney, 2004; Lago *et al.*, 2007). For example, leptin, a pro-inflammatory, adipocyte-derived type I cytokine, reduces food intake and increases energy expenditure. Conversely, deficiency of leptin or its signaling receptor (Ob-Rb) results in hyperphagia, energy thriftiness, and obesity (Halaas *et al.*, 1995; Chen *et al.*, 1996; Lago *et al.*, 2007).

In addition to these "classical cytokines", there is now strong evidence that the IL-18 also helps regulate energy homeostasis. Circulating IL-18 levels in humans positively correlate with BMI, adiposity, type 2 diabetes or insulin resistance, hypertriglyceridemia, and metabolic syndrome (Esposito *et al.*, 2002b; Esposito *et al.*, 2003; Olusi *et al.*, 2003; Hung *et al.*, 2005). Such a relationship is consistent with the chronic mild inflammatory state that accompanies obesity and associated metabolic syndrome disorders, due to increased adipocytokine release from accumulating white adipose tissue (Fain, 2006; Lago *et al.*, 2007). Indeed, "obesity-recruited" fat-resident monocyte/macrophage lineage cells are major sources of IL-18, and adipocytes from obese humans secrete 3-fold more IL-18 than those from lean donors (Skurk *et al.*, 2005; Fain, 2006). Subcutaneous adipose tissue IL-18 mRNA also is elevated in human obesity, correlating with insulin resistance (Leick *et al.*, 2007). The results suggest an adipocytokine-like action of IL-18 in obesity. Yet, and once more similar to leptin, deletion of IL-18 induces hyperphagia and late-onset body weight gain.

Here we review work carried out in mice to understand the significance of IL-18 as modulator of feeding and energy efficiency and its mechanism of action. We believe the results obtained so far serve as a valuable example of how cytokines may influence energy homeostasis.

5.1 Interleukin 18 and energy homeostasis

IL-18 is a cytokine originally identified as interferon gamma inducing factor (IGIF) in mice (Dao *et al.*, 1996) and subsequently cloned in human (Ushio *et al.*, 1996) and rat (Conti *et al.*, 1997). IL-18 has pleiotropic biological activity and is capable of modulating both the humoral or the cellular immune response depending on the cytokine milieu, influencing an exceptional variety of processes and diseases (for review, see Dinarello *et al.*, 1998; Nakanishi *et al.*, 2001). Mouse IL-18 is a 157 amino acid (aa) polypeptide produced as a 193 aa precursor matured into the secretable biologically active protein by IL1β converting enzyme (ICE). Its tertiary structure is similar to that of IL-1β (Bazan *et al.*, 1996) and its

receptor belongs to the TLR IL-1 superfamily activating the MyD88 dependent IRAK-TRAF6 pathway. Despite these similarities with IL-1β, IL-18 differs functionally from the "sickness" cytokines in key respects. For example, IL-18 is constitutively expressed, rather than being primarily inducible in response to inflammatory stimuli. Also, systemic IL-18 is not pyrogenic and can even reduce the amplitude of IL-1induced fever (Gatti *et al.*, 2002) and does not promote taste aversion (Zorrilla *et al.*, 2007). Unlike IL-1, IL-6 and TNF, IL-18 reduces food intake without producing fever or malaise. In summary, the lack of these pathologic properties and its constitutive expression place IL-18 in a position of possibly regulating food intake under non-pathological conditions and/or to be a therapeutically useful pathway for curbing food intake.

Work on the possible role of IL-18 in modulating energy homeostasis began following the observation that mice deficient for IL-18 (*Il18*$^{-/-}$) developed increased body weight gain (Ushio *et al.*, 1996; Plata-Salamán, 2001; Wallenius *et al.*, 2002; Olusi *et al.*, 2003; Wong & Pinkney, 2004; Skurk *et al.*, 2005; Thorand *et al.*, 2005; Netea *et al.*, 2006; Zorrilla *et al.*, 2007; Zorrilla & Conti, 2014). Such an increase was recorded starting at mid adulthood but not earlier and was larger in female mice. Chow-reared female *Il18*$^{-/-}$ mice weighed 27% more than WT mice at 20, but not at 15 weeks of age; male *Il18*$^{-/-}$ mice however were 14% heavier than WT mice at 27, but not at 15 weeks of age. *Il18*$^{-/-}$ mice were not only heavier, but also fatter, than age and gender matched WT mice. While brown fat mass was not disproportionately greater in *Il18*$^{-/-}$ mice, white fat pad mass of *Il18*$^{-/-}$ mice was ~ 2–3-fold greater than that of WT mice, with subcutaneous (subcutaneous, inguinal) versus intra-abdominal pads (gonadal, mesenteric, retroperitoneal) equally larger (Zorrilla *et al.*, 2007; Zorrilla & Conti, 2014).

IL-18 system deficient mice not only become fatter, but also develop steatosis associated with increased insulin levels and insulin resistance (Netea *et al.*, 2006; Zorrilla *et al.*, 2007). These data are suggestive of a late onset metabolic syndrome, which is of particular interest because it resembles what often occurs in adult humans. Circulating levels of IL-18 have consistently been reported to be elevated in patients with type 2 diabetes, and have also been suggested to contribute to nephropathy in type 2 diabetes (Aso *et al.*, 2003; Esposito *et al.*, 2003; Fischer *et al.*, 2005). Elevated levels of IL-18 have been shown to predict the development of type 2 diabetes (Esposito *et al.*, 2002a; Thorand *et al.*, 2005; Hivert *et al.*, 2009). Elevated circulating levels of IL-18 are also reported to be associated with obesity in mice.

Measurements of food intake reveal that *Il18*$^{-/-}$ mice overeat (~ 60–120% more) before they start to gain weight, indicating that increased food intake may be a cause of overweight. Hyperphagia in *Il18*$^{-/-}$ mice is larger in female mice and although no overall alteration of the circadian feeding profile is observed, both genders eat more during the late dark cycle and first three hours of the light cycle. However, this is observed only on regular (10% fat diet) but not on high (60%) fat diet where normalization per body weight eliminates any significant difference in calorie intake. These observations suggest that IL-18 may regulate lipid intake. In addition, if loss of IL-18 increases feeding, IL-18 itself may act as anorexigenic signal.

This was soon demonstrated by showing that intracerebroventricular injection of recombinant IL-18 blunted recovery of baseline body weight and re-feeding of food deprived mice in a dose dependent way. The possibility that the anorexigenic effects of recombinant IL-18 could be at least in part due to the presence of endotoxin in the preparation was tested by measuring taste aversion and fever response. The results not only excluded such possible confounding variables, but also confirmed that IL-18 could reduce food intake without inducing fever (Gatti *et al.*, 2002; Zorrilla *et al.*, 2007). Altogether these observations are indicative of the central anorexigenic action of IL-18.

Studies on cells of the immune system showed that IL-18 acts through a heterodimer receptor comprised of an alpha subunit (IL-18Rα) required for ligand interaction, and a beta subunit (IL-18Rβ) necessary for activation of signal transduction. Binding of this heterodimer complex by IL-18 induces the activation of the IL-1R-associated kinase (IRAK) transduction pathway and eventually the activation of NF-κB. The action of IL-18 is also highly regulated by negative modulators. The soluble IL-18 binding protein (IL18BP) can bind circulating IL-18 and prevent it from activating IL-18R. In addition, at least two alternative isoforms of both IL-18Rα and β have been described. One of these isoforms, arbitrarily named IL-18Rα type II to distinguish it from the canonical Type I form, lacks the intracellular toll/interleukin receptor (TIR) domain required for activation of the IRAK pathway and was thus proposed to be a decoy receptor. A short splice variant of the IL-18Rβ, previously described in rat, where it was named short IL-18Rβ (sIL-18Rβ), also exists (Alboni *et al.*, 2011). sIL-18Rβ is comprised of only one of the extracellular IgG domains of the receptor chain and it is thus believed to be a soluble form that can interfere with the dimerization of the canonical receptor complex. The full length as well as the short length and presumed negative regulators isoforms of IL-18R were all demonstrated to be expressed in neurons throughout the brain including several hypothalamic regions involved in nutrient homeostasis (Alboni *et al.*, 2009; Alboni *et al.*, 2010). In fact, high level of expression was observed in the hypothalamus, where IL-18Rα and β were found in several nuclei including the ARC, lateral hypothalamus (LH), VMH, PVN and dorsomedial (DMN) nuclei that represent important elements of nutrient sensing and major regulators of feeding and energy homeostasis. The relative distribution and amount of total, type I or type II IL-18Rα in the hypothalamus differ in specific areas and nuclei. Although it was not possible to demonstrate the localization of all isoforms, both IL-18Rβ and sIL-18Rβ are strongly induced in the brain following LPS injection indicating that the IL-18 system may modulate its central action during infection.

Hypothalamic expression of IL-18Rβ has a distribution pattern that is similar to that of IL-18Rα with especially high levels in the PVN lateral magnocellular part - PaLM, in the PVN dorsal cap - PaDC and in the ventromedial hypothalamic nucleus dorsomedial part - VMHDM. Interestingly, the levels of IL-18Rβ mRNA in the CNS are elevated following LPS.

Several questions remain to be answered to understand the exact mechanisms of action of the IL-18 system on feeding and energy efficiency. For instance, IL-18 does not readily cross the BBB and although it can be produced by microglial cells during inflammation the source of IL-18 and its ability to regulate feeding in a naïve animal remains to be determined. In

addition, despite the evidence that IL-18 may act centrally via IL-18R, IL-18 also exerted anorexigenic effects when injected intraperitoneally, indicating that peripheral mechanisms may also be at play. These may include fat-resident monocyte/macrophage lineage cells which are major source of IL-18 and also respond to it. Adipocytes from obese humans secrete 3-fold more IL-18 than those from lean donors (Skurk *et al.*, 2005; Fain, 2006) correlating with insulin resistance (Leick *et al.*, 2007) and suggesting an adipocytokine-like action of IL-18 in obesity. Interestingly, work in mice demonstrated that IL-18 is capable of affecting not only food intake but also energy efficiency. Yet how this is achieved remains to be investigated (Zorrilla *et al.*, 2007).

As mentioned above, the anorexigenic action of IL-18 is in apparent contradiction with the fact that obese individuals have increased circulating level of IL-18. In fact, circulating IL-18 levels in humans positively correlate with BMI, adiposity, type 2 diabetes or insulin resistance, hypertriglyceridemia, and metabolic syndrome (Esposito *et al.*, 2002b; Esposito *et al.*, 2003; Olusi *et al.*, 2003; Hung *et al.*, 2005). The development of IL-18 resistance was proposed as a likely explanation. One possibility is that this may occur via the negative regulators of IL-18 functions including IL-18BP, IL-18Rα type II and sIL-18Rβ, although this hypothesis remains untested. The same is true for the possible role of another member of the IL-18 family, the IL-18 binding protein (IL-18BP). IL-18BP binds IL-18 and prevents IL-18 from binding to its receptor complex thus serving as yet another negative regulator of IL-18 activity that could have a role in the development or maintenance of IL-18 resistance in obesity. Finally, the possibility that IL-18 may act during development to affect the tuning of energy homeostasis should also be considered and addressed.

Although IL-18 can contribute to the regulation of feeding also indirectly by stimulating the production of other anorexigenic cytokines such as IL-1β and TNF (Dinarello *et al.*, 1998) the information so far indicates that one of the mechanisms by which IL-18 is capable of regulating energy homeostasis is by direct action on specific brain nuclei that regulate feeding. In this respect it is a true immune-modulator of neuronal functions that may serve as communicator between the immune and the central nervous systems.

6. Conclusions and perspectives

The literature presented herein reviews the powerful impact that diet and nutrition (and the subsequent physiological responses to diet) can have on physiology and behavior; in particular, highlighting a role for the immune system as a critical link between diet and health. There is a clear and profound impact of early life nutrition, both *in utero* and in the early postnatal period, on physiology, and as reviewed here, specifically on brain development. Hypothalamic systems that underlie metabolic functions can be modulated by early life under- and overnutrition, establishing a risk for later life obesity. Additionally, other brain regions (reward circuitry, hippocampus) are affected by early life nutritional challenges, and can lead to deficits in reward related behaviors, executive function, memory and cognition. Beyond the early life time period, nutrition continues to affect health via effects on the immune system, and the literature regarding the impact of caloric restriction on immune and behavioral endpoints was summarized. Cytokines in particular have strong

effects on long term health and physiology, and one such exemplar cytokine, IL-18, was reviewed and discussed.

A number of unanswered questions remain. With regard to diet composition, there is a great deal of variance across the particular animal models. For example, some diet manipulations alter macronutrient levels (high fat or low protein), while others hold the diet composition constant, and alter the amounts (e.g., 50% of *ad libitum* levels, or altering litter size in the early neonatal studies). It is also important to parse out the relative contributions of the diet *per se*, as opposed to the response to the diet (e.g., an effect of a high fat diet versus the resultant obesity with increases in adipokines and cytokines). However, the strength of these multiple approaches emerges as convergent findings are documented across divergent models. Another area that requires additional focus is the functioning of specific barriers (e.g., the BBB and the maternal-fetal divide within the placenta) in communicating information. Whether cytokines pass through these barriers and/or act directly on these barriers at specific points of development requires additional clarification. And the same questions apply to the trafficking of immune cells, which can themselves secrete cytokines.

Because diet and nutrition are modifiable variables, a better understanding of their effects on the immune system and how these effects underlie related physiological changes (obesity, behavior) is critical. Modification of diet represents not only a therapeutic strategy for the treatment of a wide range of poor health outcomes, but should remain a focus of preventative health strategies and the establishment of optimal health and resilience.

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Abbreviations

ACTH	adrenocorticotropic hormone
ARC	arcuate nucleus
BDNF	brain derived neurotropic factor
BMI	body mass index
CR	calorie restriction
CRH	corticotropin-releasing hormone
GR	glucocorticoid receptor
HPA axis	hypothalamic-pituitary-adrenal axis
IF	intermittent fasting
IκB	inhibitory factor κB

IL	interleukin
Iba1	ionized calcium-binding adapter molecule
LPS	lipopolysaccharide
NHP	nonhuman primate
NFκB	nuclear factor κB
PVN	paraventricular nucleus of the hypothalamus, poly I:C, polyinosinic:polycytidylic acid
POMC	pro-opiomelanocortin
TLR	toll-like receptor
WT	wild type

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Diet, behavior and immunity across the lifespan

- Undernutrition and overnutrition, perinatally and throughout life, cause increased risk for obesity and metabolic disorders
- Nutrition also influences adverse mental health outcomes.
- The immune system is critical in this programming, linking diet with long term health and behavioral outcomes.

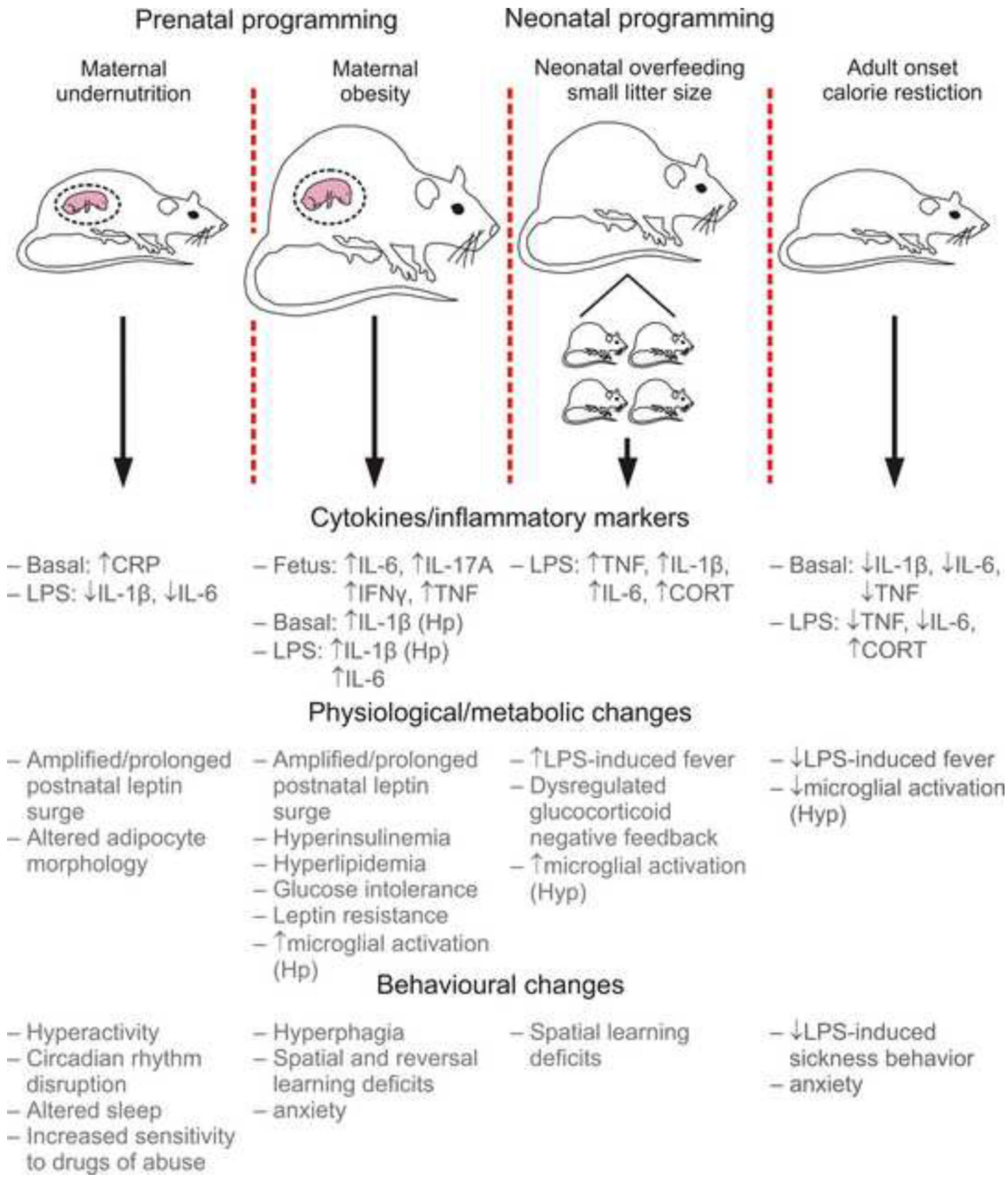

Figure 1.

Exposure to maternal under- or over-nutrition during gestation, or early life overfeeding can have life-long consequences for immune system functioning, metabolism and behavior. The schematic illustrates two rodent models of prenatal programming, maternal undernutrition and maternal obesity; and one rodent model of neonatal programming, suckling rats in small litters, along with some examples of the physiological, metabolic, and behavioral changes that occur as a result. The schematic also illustrates a model of adult onset calorie restriction, which can have a number of health promoting benefits.

Abbreviations: CORT, corticosterone; CRP, C-reactive-protein; Hp, hippocampus; Hyp, hypothalamus; LPS, lipopolysaccharide; TNF, tumor necrosis factor