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Review article

Glucocorticoid programming of neuroimmune function

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ABSTRACT

Throughout life physiological systems strive to maintain homeostasis and these systems are susceptible to exposure to maternal or environmental perturbations, particularly during embryonic development. In some cases, these perturbations may influence genetic and physiological processes that permanently alter the functioning of these physiological systems; a process known as developmental programming. In recent years, the neuroimmune system has garnered attention for its fundamental interactions with key hormonal systems, such as the hypothalamic pituitary adrenal (HPA) axis. The ultimate product of this axis, the glucocorticoid hormones, play a key role in modulating immune responses within the periphery and the CNS as part of the physiological stress response. It is well-established that elevated glucocorticoids induced by developmental stress exert profound short and long-term physiological effects, yet there is relatively little information of how these effects are manifested within the neuroimmune system. Pre and post-natal periods are prime candidates for manipulation in order to uncover the physiological mechanisms that underlie glucocorticoid programming of neuroimmune responses. Understanding the potential programming role of glucocorticoids may be key in uncovering vulnerable windows of CNS susceptibility to stressful experiences during embryonic development and improve our use of glucocorticoids as therapeutics in the treatment of neurodegenerative diseases.

1. Introduction

Early life experiences have the power to modify a myriad of neuroendocrine and physiological systems. For example, it has been well documented that exposure to adverse conditions during development can cause alterations to the functioning of axes such as the hypothalamic pituitary adrenal (HPA) axis, responsible for the physiological response to stress in all vertebrate animals (Aisa et al., 2008; Spencer et al., 2009; Turecki, 2014). It is well established that HPA axis activation induces physiological changes and behaviours that promote short-term survival (Wingfield and Romero, 2010). However, sometimes these effects persist into adulthood, and in many cases developmental adversity can produce negative maladaptive results, increasing the risk of several health and disease pathologies, (Lin et al., 2016; Mpofana et al., 2016). Disruption of the normal development of such axes can also have significant downstream effects on other physiological systems (Xiong and Zhang, 2013; Gold, 2015; Kinlein et al., 2015). In particular, exposure to stressful stimuli during development has significant effects on the immune system (Ziv et al., 2006; Chen et al., 2011; Fagundes et al., 2013). As such, there is significant interplay between the 'stress' and immune responses within both peripheral tissues and the central nervous system (CNS), as both act in different ways to maintain homeostatic processes within the organism (Silverman et al., 2005).

Peripheral tissues harbour a wide variety of leukocytes which play a key role in both innate and adaptive immune responses, while the CNS possesses its own specialised population of innate immune cells called microglia. These specialised macrophages form the basis of the neuroimmune system and function to protect neurons from invading pathogens. In response to cerebral insults, microglia secrete a variety of inflammatory molecules, such as cytokines (Felger and Lotrich, 2013), which can stimulate neuronal activity within the paraventricular nucleus (PVN) of the hypothalamus to activate the HPA axis. This suggests that there may be a direct physical interaction between immune cells and the HPA axis cascade within the CNS, thus distinguishing the neuroimmune system from its peripheral counterpart. However, the mechanism by which this interaction may occur is unclear. One candidate mechanism may be the negative feedback action of glucocorticoid hormones, which tightly regulate both the duration and magnitude of stress and immune responses in order to restore homeostasis (Franchimont, 2004; Coutinho and Chapman, 2011). The complex interaction between these systems suggests that early life experiences and the potential elevations in glucocorticoid levels, may

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have the power to program how well the neuroimmune system functions in later life. Indeed there is tantalising evidence in favour of this, as we will discuss as part of this review (Shanks and Lightman, 2001; Bilbo and Schwarz, 2009). However, it is currently unclear if the effects of early life are mediated by the direct effects of glucocorticoids on neuroimmune activity or if the downstream effects on HPA functioning also constrain the neuroimmune system.

In this mini-review, we discuss the potential programming effects of early life exposure to stressful stimuli on the long-term functioning of the neuroimmune system. We first explore the importance of the neuroimmune response and the role of microglia, the resident innate immune cells that maintain this system. We then go on to discuss the way in which the neuroimmune system interacts with the HPA axis and follow this up with an in-depth discussion of the potential for developmental programming of glucocorticoids and microglia function and other CNS components. We aim to provide a framework for future research directions in order to facilitate more work in this unexplored area.

1.1. The neuroimmune system and its importance for health and disease

The neuroimmune system comprises both the CNS and the immune systems, which act in synchrony to protect the host from localised pathogenic attack and subsequent disease. The CNS is often endowed an "immune-privileged" status due to its comparative isolation from the periphery, the lack of efficient antigen presenting cells and until recently, the absence of a lymphatic drainage system. Recent evidence has revealed that dural sinuses and meningeal vessels within the brain are lined with lymphatic vessels that are capable of transporting immune cells via the cerebrospinal fluid to deep cervical lymph nodes (Aspelund et al., 2015; Louveau et al., 2015a). It has since been postulated that these lymphatic vessels may be essential for the CNS to be capable of mounting its own innate response to infection but this could also be the primary route for interaction with the periphery (Louveau et al., 2015b).

The first line of neuroimmune defence in response to localised infection is microglia cells, which comprise 10–15% of cells within the CNS (Lawson et al., 1992). Microglia originate as myeloid cell progenitors in the yolk sac (Ginhoux et al., 2010) and undergo rapid expansion and colonisation into neural tissue during the post-natal period and continue to develop until adulthood (Bilbo et al., 2012). The peripheral origin of microglia is consistent across taxa, as described in zebrafish (*Danio rerio*) (Herbomel et al., 2001) and avian species (Cuadros and Navascués, 1998), but migratory paths to the CNS appear to vary. In mammals, microglia migration occurs during the first two trimesters, where phagocytic glia are detectable as early as the 8th–12th week of embryonic development and are capable of secreting cytokines and free radicals (Beauvillain et al., 2008; Tardieu, 2013). In birds, microglia are detectable in the avian CNS between embryonic days 7–16 (Carrasco et al., 2011) and studies in quail have revealed that microglia can also colonise regions of the CNS such as the optic tectum (Cuadros et al., 1994), cerebellum (Cuadros et al., 1997) and the retina (Marin-Teva et al., 1998) via the brain ventricles or across the meninges (Cuadros and Navascués, 1998).

Under basal conditions, microglia survey particulate matter present within the blood (Glenn et al., 1992; Dudvarski Stankovic et al., 2016). Once activated, microglia can freely move throughout the CNS clearing cellular debris and apoptotic cells before congregating around the site of infection where they function as efficient antigen presenting cells (Shaked et al., 2004) to naïve T lymphocytes migrating across the blood-brain barrier (BBB) (Suter et al., 2003). This interaction results in a positive feedback mechanism between microglia and T cells that has recently been linked to the onset of neurodegenerative diseases such as Multiple Sclerosis (Strachan-Whaley et al., 2014) and Experimental Autoimmune Encephalomyelitis (EAE) (Cherry et al., 2014). Microglia also play a key role in regulating neuronal and synaptic plasticity (Norden and Godbout, 2013; Wu et al., 2015) while degenerating neurons in turn can promote the neuroprotective function of microglia. This is achieved through the binding of the neuronal chemokine, CX3CL1, with its corresponding receptor, CX3CR1, on microglia, resulting in inhibited pro-inflammatory cytokine production and increased microglia clearance of cellular debris (Noda et al., 2011). This dynamic property of microglia allows them and neighbouring neurons to modulate each other's activity in order to maintain homeostasis as part of the neuroimmune system (Eyo and Wu, 2013). This dual role of microglia has recently received attention as a way to uncover the mechanisms that regulate the switch between these neurotoxic pro-inflammatory (M1) and neuroprotective anti-inflammatory phenotypes (M2) (Schwarz and Bilbo, 2013; Block, 2016), so that microglia activity could be regulated therapeutically (Zhou et al., 2014). As such, there is extensive clinical and experimental research that links neuroinflammation and microglia function with several neurodegenerative disease pathologies. In cases of Alzheimer's disease, microglia congregate around amyloid plaques and phagocytose its protein product, Amyloid β (Stalder et al., 1999; Lee and Landreth, 2010). In addition these cells potently secrete inflammatory molecules during spinal cord trauma (Zhou et al., 2014), chronic infectious diseases such as prion disease (Eikelenboom et al., 2002) and tuberculosis (Spanos et al., 2015). In addition to maintaining normal CNS functioning and preventing the onset of these aforementioned pathologies, the neuroimmune system requires communication from other physiological systems in order to maintain whole-body homeostasis.

1.2. Neuroimmune and neuroendocrine interactions

Microglia are present within all CNS tissues associated with HPA axis functioning and secrete cytokines in an autocrine fashion that synergistically stimulates HPA axis activity (O'Connor et al., 2000) (Fig. 1). Pro-inflammatory cytokines, particularly interleukins 1 (IL-1), 6 (IL-6) and tumour necrosis factor (TNF-α), predominantly emanate from microglia to potently induce glucocorticoid secretion during stress or immune responses (Felger and Lotrich, 2013). Glucocorticoids classically function to suppress both stress and immune responses by binding with specific glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) in cells of the CNS and immune tissues such as the thymus and spleen (Miller et al., 1998). GR is ubiquitously expressed throughout the CNS with high levels of expression in neurons and microglia (Sorrells et al., 2009), while MR expression is confined to a few regions, such as the hippocampus, amygdala and neurons within the PVN of the hypothalamus (Reul and de Kloet, 1985; Vyas et al., 2016). MR possess a binding affinity to glucocorticoids that is five to ten fold higher than GR (De Kloet et al., 1998) and these differences in receptor binding affinities are thought to influence the dynamic modulation of the stress response (Oitzl et al., 2010) but in some cases GR and MR appear to mediate different effects on immune system functioning (McEwen et al., 1997; Lattin et al., 2013). MR binding of basal glucocorticoids may induce pro-inflammatory effects (Lim et al., 2007; Harizi et al., 2008), while the majority anti-inflammatory effects of glucocorticoids occur either directly or indirectly via GR binding (McEwen et al., 1997). Under basal conditions, MR modulate feedback regulation and determine the sensitivity of the HPA axis to stressful stimuli allowing for the selection of the appropriate behavioural strategy to cope with the effects induced by the stressor (Matthews,

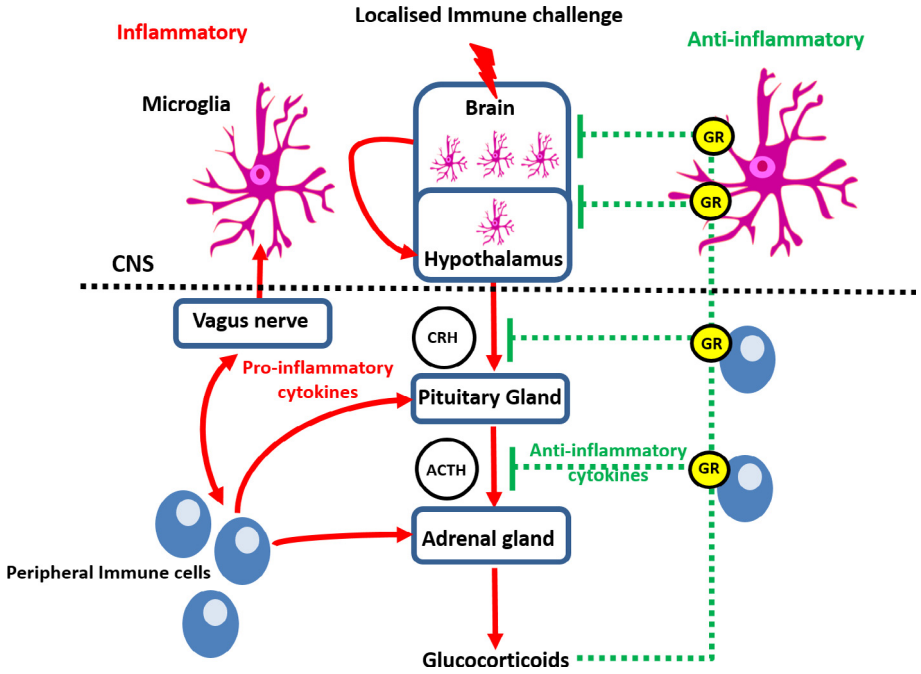

Fig. 1. Regulation of immune responses via HPA axis activation. During the immune response, pro-inflammatory cytokines are predominantly secreted by microglia in the CNS which activate the HPA axis from the hypothalamus (red arrows). Peripheral immune cells secrete pro-inflammatory cytokines which act at all three levels of the HPA axis, including microglia in the CNS via activation of the vagus nerve. Glucocorticoids regulate negative feedback of both peripheral and CNS immune responses by binding to glucocorticoid receptors in immune cells. This receptor complex promotes the transcription of anti-inflammatory cytokines, which act at all levels of the HPA axis to inhibit further release of CRH and ACTH from the hypothalamus and the pituitary gland respectively (dashed green lines).

2002; Joels et al., 2008). When glucocorticoid levels increase after exposure to stress or peaks of ultradian rhythm (Conway-Campbell et al., 2007), the main glucocorticoid stress hormone, corticosterone (CORT), activates GR. This complex then translocates to cell nuclei and interacts with transcription factors such as Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-κB) (Rivest, 2001) and Activating Protein 1 (AP-1) (Barnes, 1998) to promote the transcription of anti-inflammatory cytokines, such as IL-4 and IL-10. These cytokines and other anti-inflammatory mediators inhibit pro-inflammatory cytokine release from microglia within the CNS and immune cells circulating in the periphery, thereby protecting the host from an overactive immune response. However, the transcriptional effects of glucocorticoids appear to have varying effects on microglia activity. Nair and Bonneau (2006), proposed a mechanism whereby stress-induced glucocorticoid secretion enhances microglia proliferation in response to upstream neurostimulation of GR. This mechanism involves the accumulation of extracellular glutamate that induces neuronal N-methyl-D-aspartate (NMDA) receptor activity to secrete a suite of pro-inflammatory mediators, which are thought to contribute to stress-induced microglia proliferation. Furthermore, increased NF-κB signalling restricts microglia pathological activity (Kreutzberg, 1996; Nair et al., 2008) but can also contribute to neuronal survival (Camandola and Mattson, 2007). Circulating peripheral cytokines can also trigger neuroimmune responses via stimulation of the vagus nerve that impacts on the autonomic nervous system and pathways related to sickness behaviour (Jang and Johnson, 2010). Activation of the vagus nerve stimulates microglia activity to produce cytokines via the central adrenergic system to innervate several lymphoid tissues such as the bone marrow and spleen (Laye et al., 1995; Bilbo et al., 2012).

Recent studies suggest that neuroimmune function is also modulated by circadian rhythms and sex hormones. The discovery of clock genes within microglia, coupled with their rhythmic basal expression of cytokines suggests that microglia are primed to face inflammatory challenges throughout the day (Fonken et al., 2015). This "long photoperiodic immune phenotype" enables cytokines to transiently re-direct the synthesis of photoperiodic hormones, such as melatonin, to act on circulating macrophages (Markus et al., 2013). This interaction reverses their immune-enhancing function by inhibiting cytokine production via NF-κB signalling (Weil et al., 2015). Sex hormones also exert differential effects on microglia that are both age and sex-dependent. In female neonatal rats (*Rattus norvegicus*), estradiol promotes pro-inflammatory responses by microglia (via IL-1β expression) which contrasts with anti-inflammatory effects observed in males. However, in adulthood, estradiol induces pro-inflammatory effects regardless of sex differences (Loram et al., 2012). This revelation complements the distinct morphological, phenotypic and epigenetic profiles displayed by microglia during development (Bilbo et al., 2012).

1.3. Developmental programming of the neuroimmune system

The concept of programming proposes that early life events can permanently influence later physiological and behavioural phenotypes in a way that impacts on the health of both the afflicted individual and its offspring (Welberg and Seckl, 2001; Barker, 2004). These events stem from both maternal and environmental factors and have multi-faceted biological effects that extend across taxa (Schoech et al., 2011). In amniotic vertebrates, stress-exposed mothers are capable of altering the sensitivity of their offspring to stressors through the maternal transfer of antibodies (Grindstaff et al., 2003; Hasselquist and Nilsson, 2009) and glucocorticoid hormones (Groothuis and Schwabl, 2008) into the placenta in mammals or the yolk or albumen in egg-laying vertebrates (Hasselquist et al., 2012; Brown and Shine, 2016). There is some debate as to when the negative feedback role of glucocorticoids is established. Early indications suggest that this mechanism is programmed during either pre-natal or post-natal periods (Meaney et al., 1985; Reichardt and Schutz, 1996).

However, studies in birds have revealed that the onset and rate at which negative feedback is achieved may vary with environmental and seasonal changes as well as breeding conditions (Boonstra, 2004; Lattin et al., 2012; Krause et al., 2016), and these shifts in recovery rates may have profound effects on immune function. To date, only one study to date has explored this hypothesis. Schmidt et al. (2012), showed male song sparrows (*Melospiza melodia*) that possessed a more efficient negative feedback over their contemporaries had a lower heterophil to lymphocyte ratio in their blood, indicating reduced physiological stress or infection. However, measuring heterophil to lymphocyte ratio does not reliably infer the dynamics of the immune response and while stress response measurements (plasma CORT) are measured instantaneously, the heterophil to lymphocyte is an indicator of stress over a prolonged period and may be not be indicative of HPA negative feedback efficacy, at least in avian species (Vleck et al., 2000; Moreno et al., 2002; Müller et al., 2011).

Taken together, the data produced from experimental manipulation of glucocorticoid levels during the highly sensitive developmental periods demonstrates long lasting effects that are well documented to impact negatively on physiology and behaviour (Sapolsky, 2000; Seckl, 2004; Monaghan and Haussmann, 2015). Yet surprisingly, the majority of studies investigating the influence of developmental adversity on neuroimmune function tend to focus on short-term physiological and behavioural effects. These studies utilise stress-induced paradigms such as maternal separation (Barreau et al., 2004; Gracia-Rubio et al., 2016) neonatal food restriction (Spencer, 2013; Bolton and Bilbo, 2014) and peripheral infection with a bacterial pathogen, such as lipopolysaccharide (LPS) or *Escherichia coli* (*E. coli*) (Bilbo et al., 2007; Ortega et al., 2011). These treatments typically enhance microglia activity, elevate pro-inflammatory cytokines and increase peripheral CORT within hours of the treatment (see Hoeijmakers et al. (2016) for an extensive review). This leads to heightened HPA axis activity and neuroinflammation. Aside from these short-term effects, it has also been suggested that some aspects persist into adulthood, where neonatal rats infected with LPS exhibit exaggerated microglia activity and pro-inflammatory cytokine expression within limbic regions of the brain such as the hippocampus (Wang et al., 2013). These exaggerated physiological changes are known to correlate with the onset of anxiety-like behaviours and cognitive impairments in adolescence and adulthood (Dinel et al., 2014) and can influence underlying reproductive behaviours such as song production in passerine species (Bischoff et al., 2009). The mechanisms which underlie these long-term changes in microglia are poorly understood but one common view is that epigenetic regulation of GR may play a role (Meaney and Szyf, 2005). DNA methylation of the GR promoter increases GR expression in limbic regions of the CNS such as the hippocampus and amygdala (Weaver et al., 2004; Bolton and Bilbo, 2014), which subsequently increases downstream NF-κB mediated cytokine signalling from immune cells. These physiological changes accompany the development of anxiety-like behaviours, anhedonia (Ślusarczyk et al., 2015) and neuroanatomical abnormalities in these regions, resulting in impaired cognitive and reproductive performance (Vallée et al., 1999; Spencer et al., 2005; Henriksen et al., 2011).

In terms of direct effects on neuroimmune system functioning, glucocorticoids directly modulate both the neurotoxic and neuroprotective function of microglia through interaction with both GR and MR expressed by microglia (Tanaka et al., 1997; Gómez-González and Escobar, 2010). Studies in rodents have demonstrated *in vivo* that CORT sensitises hippocampal microglia to subsequent immune challenges *ex vivo* (Sorrells et al., 2009; Frank et al., 2010), which is thought to be induced by the priming effects of CORT on cytokine responses (Frank et al., 2012). This work has been extended to models of spinal neuroinflammation, where CORT sensitises spinal microglia to subsequent LPS infection by potentiating their pro-inflammatory responses (Loram et al., 2011). In contrast to these early life programming effects, studies such as those by Frank et al. (2010) have demonstrated activational effects of glucocorticoids upon prior exposure to infection. Adult rats exposed to glucocorticoids one hour after LPS infection exhibit anti-inflammatory effects within the CNS, such as inhibition of IL-1β and TNFα expression. Therefore, the timing between glucocorticoid production and immune challenge appears to be crucial if glucocorticoids are to mediate neuroimmune function. Additionally, pre-natal immunization with LPS elevates basal CORT in the adult offspring, which accompanies reduced binding affinities with GR in HPA axis-associated tissues within the CNS (Reul et al., 1994). However, these same treatments can also prime cytokine secretion from microglia within HPA axis tissues to increase basal glucocorticoid secretion in order to sensitise leukocytes to the effects of glucocorticoid secretion in adulthood (Shanks et al., 2000; Frank et al., 2007). These data further highlight that the magnitude of glucocorticoid production induced by microglia may be dependent on the type of stressor experienced. However, the majority of immune programming studies tend to focus solely on the programming effects of the pathogen itself rather than the potential indirect programming effects of elevated glucocorticoids induced from early life infection.

Interestingly, studies in birds have demonstrated that maternal transfer of glucocorticoid hormones and their subsequent action on immune responses appear to be highly context-dependent on the type of stressor experienced by the mother or offspring. Manipulations using exogenous CORT via implant dampens T-cell mediated immune responsiveness in female common eider ducks (*Somateria mollissima*) (Bourgeon and Raclot, 2006), while zebra finches selectively bred to produce elevated CORT show increased cell-mediated responses (Roberts et al., 2007). These observations highlight glucocorticoids as prime targets for studies of early life programming of both HPA axis and immune system activity. However, the few studies demonstrating this potential provide data from immune responses within peripheral tissue and therefore, this may not reflect neuroimmune activity.

To tease apart these ambiguous results, it may be necessary to determine the direct effects of elevated glucocorticoids on the dynamics of the microglia neuroimmune response throughout lifespan. However, the current literature is conflicting as it appears that stress-induced elevations in glucocorticoids are capable of priming both short and long-term pro-inflammatory M1 and anti-inflammatory M2 microglia phenotypes within specific CNS regions, depending upon the type of stressor exposed to during development (Fig. 2). For example, immediate increases in glucocorticoid exposure following cortisone treatment and *E. coli* infection increases M1 microglia activation in the hippocampus and corpus callosum respectively (McRae et al., 1996; Lieblein-Boff et al., 2013) while other studies report reduced M1 microglia activity and inhibited expression of inflammatory mediators in the hypothalamus and hippocampus in response to maternal separation (Wei et al., 2012; Delpech et al., 2016; Roque et al., 2016). Maternal separation, neonatal food restriction and immune challenges induce prolonged M1 microglia activation in the hippocampus via enhanced cytokine and Iba1 protein expression (Bilbo et al., 2005; Galic et al., 2008; Sadagurski et al., 2015; Markovi et al., 2017). Conversely, Burke et al. (2013) reported no long-term activational changes in microglia within the hippocampus and prefrontal cortex following maternal separation. However, other studies have reported reduced M1 microglia activity in the hypothalamus following neonatal LPS exposure (Iwasa et al., 2009) and suppressed microglia responses to seizure-induced hippocampal damages following neonatal food restriction (Lee et al., 2003). Several studies also indicate that these changes in M1 and

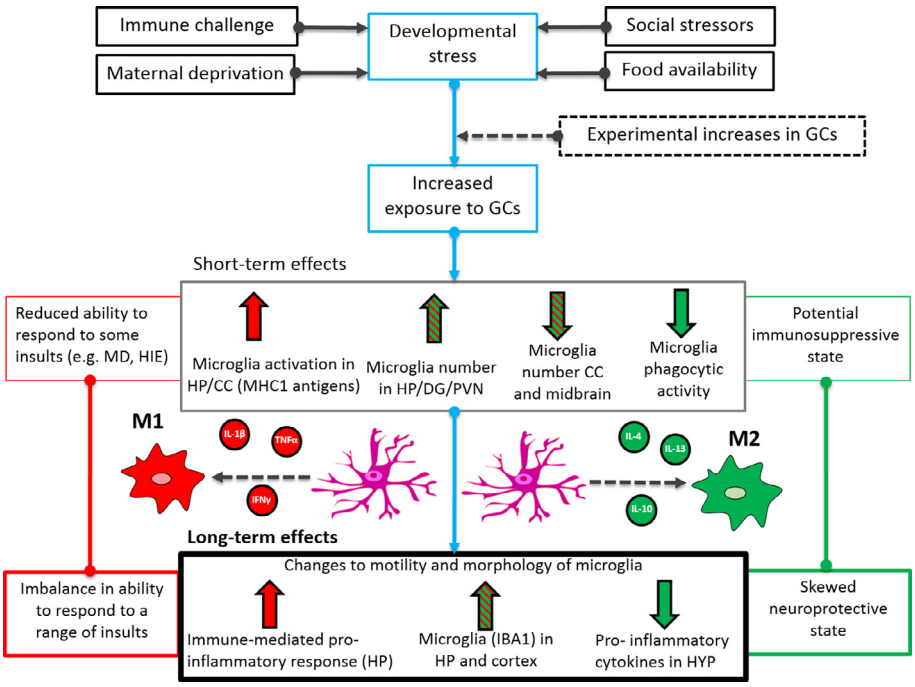

Fig. 2. Overview of the short and long-term effects of elevated glucocorticoids during development on microglia functioning. Various environmental and maternal factors cause developmental stress such as maternal deprivation, food restriction, social stressors and immune challenge. Several studies have also manipulated glucocorticoid (GCs) levels to *in utero* or *in ovo* to simulate developmental stress (dashed box and arrow). Stress exposure results in immediate HPA axis activation and elevations in endogenous GCs which have differing short and long-term effects on microglia proliferation and activity within the CNS depending on the type of stressor exposed to. Both pro-inflammatory (red arrows) and anti-inflammatory (green arrows) effects are observed, however evidence from studies in cell number don't indicate which phenotype microglia predominantly occupy (red & green patterned arrows). The short and long-term effects of elevated GCs during development accompany transitional changes in microglia between the inflammatory M1 and anti-inflammatory M2 phenotypes which are mediated by cytokines. Taken together, elevated GCs can program both pro (red boxes) and anti-inflammatory (green boxes) effects on neuroimmune system functioning. Abbreviations: CC (corpus callosum); DG (dentate gyrus); GCs (glucocorticoids); HIE (hypoxic ischemia); HP (hippocampus); MD (maternal deprivation); MHC1 (major histocompatibility complex 1); PVN (paraventricular nucleus of the hypothalamus). Citations: Bilbo et al. (2005), Bland et al., (2010), Chocyk et al., (2011), Delpech et al., (2016), Diz-Chaves et al., (2012), Galic et al., (2008), Iwasa et al., (2009), Lee et al., (2003), Lieblein-Boff et al., (2013), Kaur et al., (1994), Markovi et al., (2017), McRae et al., (1996), Roque et al., (2016), Sidor et al., (2014), Takatsuru et al., (2015), Tu et al., (2012), Wei et al., (2012).

M2 microglia phenotypes may be driven by changes in microglia cell density. New-born rats subjected to CORT treatment exhibit a 40–60% reduction in the number of amoeboid microglia in the corpus callosum by the first postnatal week (Wu et al., 2001). In contrast, neonatal separation in rats for a period of 10 days increases microglia distribution in the vagus nerve and the brainstem (Baldy et al., 2016). Rats infected with LPS during postnatal days 3 and 5 exhibit sex-specific increases in microglia number within the PVN of the hypothalamus and the dorsal raphe by post-natal day 21 (Sidor et al., 2014). Further experiments exposing rats to synthetic glucocorticoids, such as dexamethasone, during the postnatal period lead to impairments in microglia proliferation and increased microglia cell death (Wu et al., 2001). Gomez-Gonzalez and Escobar (2009) further elaborated on these findings by demonstrating that exogenously administered glucocorticoids bind to both low and high affinity GRs expressed in microglia in pre-natally stressed rats, which may perturb BBB formation and permeability by delaying angiogenesis (Wolff et al., 1992). In contrast, other studies postulate that glucocorticoids act directly on brain endothelia and interact with adjacent microglia to induce tight junction development to improve BBB permeability (Raub, 1996; Stonestreet et al., 1999) to allow the passage of migratory T cells for interaction with antigen presenting cells in the CNS (Suter et al., 2003). Several studies have pinpointed that microglia activation disrupts BBB function by releasing molecules that induce hyperpermeability and inflammation (da Fonseca et al., 2014). It may be that the immunosuppressant role of glucocorticoids also indirectly reduce microglia activation by restricting permeability of the BBB. These studies provide concrete evidence that developmental stress alters microglia abundance in the aged brain (Gómez-González and Escobar, 2010), yet there is no evidence present to suggest that this arose from alterations in the prior ability of microglia to migrate and colonise the CNS during embryonic development.

1.4. The adaptive potential for glucocorticoid programming

The physiological and behavioural effects of developmental stress on the adult neuroimmune phenotype appear to be highly dependent on three main parameters. Firstly, the type of stressor the individual is subjected to; secondly, the duration at which the individual is exposed to stress during development (Cottrell and Seckl, 2009; Kapoor et al., 2009; Brunton and Russell, 2010); and thirdly, in some cases, the sex of the individual itself (Mueller and Bale, 2007; Caetano et al., 2016). These factors may influence the magnitude of glucocorticoid release during development such that glucocorticoids may alter the long-term neuroimmune phenotype, such as the accelerating the transition of microglia from its pro-inflammatory state (M1) to its alternatively activated or anti-inflammatory state (M2) (Bilbo and Schwarz, 2009; Cherry et al., 2014). Therefore, assessing the differences in the levels of stress-induced glucocorticoid production in early life may give an indication of how these immunosuppressive molecules could potentially program both pro and anti-inflammatory microglia responses to a subsequent stress exposure.

The majority of immune programming studies focus on manipulation of maternal and environmental factors, yet relatively little work has elucidated a role for early psychological stress in programming long-term neuroimmune function. However, Wohleb et al. (2013), utilised a social stress paradigm in mice

(*Mus musculus*) to demonstrate that repeated social defeat induces spleen-derived myeloid cells to colonise limbic regions of the brain and differentiate into microglia-like cells and increase neuroinflammation. This correlates with the prolongation of anxiety-like behaviours, thus suggesting that psychological and social stressors are capable of programming neuroimmune function. These studies also tend to focus on the long-term effects of developmental stress at either the pre or post-natal stage as they are considered as vulnerable windows of development, yet there is evidence to suggest that stress or immune challenge exposure at multiple stages during life can have cumulative and transgenerational effects on physiology and behaviour that are potentially adaptive (Grindstaff et al., 2006; Goerlich et al., 2012; Ericsson et al., 2016). In an ecological context, natural selection should favour individuals with more efficient immune responses that are able to withstand the harsh early environment, but this may trade-off against long-term survival (Williams, 1957; Hayward et al., 2016). Such a trade-off has been demonstrated in passerines where individuals can invest in immune defence at the expense of growth (Soler et al., 2003; Brommer, 2004; Tschirren et al., 2009). It is important to highlight that the emergence of such a trade-off within an individual may be affected if the effects of glucocorticoid programming are transmitted from the parent to the offspring, should the offspring be programmed to mount efficient immune responses and show long-term survival (Goerlich et al., 2012). To the best of our knowledge, there is no research that considers the cumulative effects of immune challenges on adult neuroimmune phenotype such that early life adversity can program stronger neuroimmune responses and promote adaptive behaviours to subsequent immune challenges that are fitness enhancing. Further research into the interactive effects of developmental programming at different life stages and its long-term effects on neuroimmune function are therefore required.

2. Conclusions

Developmental programming of the neuroimmune system remains a relatively new field of study but it is clear that glucocorticoids are a prime target for research as they act as the functional molecular link between stress and both CNS and peripheral immune responses. To gain a better understanding of neuroimmune programming, we must be able to determine the specific developmental stage at which the architecture of the neuroimmune system is most susceptible to both direct and indirect glucocorticoid action. As glucocorticoids are capable of increasing the susceptibility of the CNS to stressful events, we should also consider that this may be mediated by the interaction with maternal and environmental stressors throughout an individual's life history. Such studies require careful monitoring of the individual throughout its life and therefore the ideal approach would be to carry out comparative studies across several species. As stress and infection can be encountered multiple times during life we should also consider the cumulative effects of repeated stress or infection on neuroimmune responses and how this may or may not impact on pre-programmed responses established earlier in development. Such studies will allow us to distinguish the beneficial and detrimental effects of developmental programming on neuroimmune function and improve our ability to develop new therapeutic strategies.

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