6 Neuroendocrine-immune Interactions in Major Depressive Disorder: Glucocorticoids and Glucocorticoid Receptors

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Abstract

Major depressive disorder is a leading cause of disability worldwide; therefore, effective treatment options are crucial. However, due to the highly heterogeneous nature of depression, a comprehensive understanding of the disease is lacking and treatment options are limited. Whilst the pathology of depression is complex, neuroendocrine–immune interactions have consistently been linked to the disease. Hypothalamic–pituitary–adrenal (HPA) axis dysfunction has been identified as one of the main contributing factors, impacting 50–80% of patients with depression. The 'glucocorticoid resistance model' provided the first explanations of this dysfunction, suggesting reduced function of the glucocorticoid receptor; thus, glucocorticoid resistance, seen in some MDD patients, allows pro-inflammatory pathways to evade normal feedback inhibition by glucocorticoids. However, recent research has suggested alternative mechanisms, which identify cortisol as a pro-inflammatory mediator of stress reactions.

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Additional research into glucocorticoid dysfunction in MDD has also found single nucleotide polymorphisms in FKBP5, a key regulator of glucocorticoid receptor function, to play a role in HPA axis dysfunction and thus confer risk of depression. These effects are mediated by gene–environment interactions, specifically adverse early-life events. Whilst the underlying epigenetic mechanisms are not fully understood, increased FKBP5 mRNA expression and altered FKBP5 methylation are thought to play a role in impaired HPA axis function. An increased understanding of the interactions involving FKBP5 may in turn increase understanding of the pathophysiology of depression. This will allow identification of high-risk individuals who have past adverse early-life experiences. In turn, this may also impact the course of future antidepressant treatment and development.

Keywords

Major depressive disorder · Hypothalamic–pituitary–adrenal axis · Glucocorticoids · Glucocorticoid resistance · Inflammation · FKBP5 · Neuroendocrine immunology

6.1 Introduction

In recent decades, there has been a growing body of evidence for the association between the physiological functioning of the body and psychiatric state (Renoir et al. 2013). One of the best-established pathways involved in this mind–body interface is the neuroendocrine system, involving communication between the endocrine and nervous system (Toni 2004). This interaction is crucial for regulating homeostasis within the body; thus, a deviation in normal endocrine function can cause multiple pathological consequences.

One of the most researched neuroendocrine pathways involved in this mind–body interface is the hypothalamic–pituitary–adrenal (HPA) axis. HPA axis homeostasis is an integral component in maintaining a normal stress response, and directly influences the central nervous system, coordinating emotional, behavioural and physiological events (Seidman 2006). HPA axis activation triggers the release of the glucocorticoid hormone, cortisol (humans) or corticosterone (rodents), which plays a crucial role in anti-inflammatory and immunosuppressive processes required for maintaining homeostasis (Bellavance and Rivest 2014). Glucocorticoid receptors (GRs) are expressed on nearly all immune cell types; therefore, glucocorticoids have a wide range of immunomodulatory functions.

Extensive research has identified an association between HPA axis dysregulation and immune dysregulation, with psychiatric conditions such as major depressive disorder (MDD). Interestingly, the two most frequently reported physiological findings in MDD are HPA axis hyperactivation and increased inflammation (Pariante 2017). This is particularly important as MDD is currently the leading cause of disability around the world, increased in prevalence by 18.4% between

2005 and 2015 (Friedrich 2017), and was the largest contributor to nonfatal health loss in 2015 (Friedrich 2017). Furthermore, MDD is associated with the development of heart diseases, diabetes and stroke, and an increased risk of developing Alzheimer's disease (Lang and Borgwardt 2013). However, despite this impact, treatment options are still largely ineffective. Over 50% of patients do not respond to the first treatment prescribed, whilst 30% still do not respond following multiple different treatment attempts (Menke 2019). Individuals who do not respond or respond partially to treatments may be considered as having 'treatment-resistant' or 'partially responsive' depression, respectively (Sforzini et al. 2021). Therefore, MDD is currently a major mental and public health issue, and identifying its biomarkers is crucial to future successful treatment regimes (Mäntylä 2020).

Around 50–80% of depressed patients show hyperactivity of the HPA axis and glucocorticoid resistance (Anacker et al. 2011). However, to be able to stabilise this hyperactivity or identify patients most at risk to it, researchers must identify the causes. 'Glucocorticoid resistance' expresses the concept that glucocorticoid hormones are unable to exert their physiological actions, including the feedback inhibition on cortisol secretion and the anti-inflammatory action (see below). Thus, the role of GR resistance and its interplay with increased inflammation in MDD has been identified as an area of interest for research (Cattaneo et al. 2020).

In the search for molecular targets of HPA axis dysregulation in MDD, FK506 binding protein 51 (FKBP5), a key regulator of the GR, has been identified (Rao et al. 2016). Specifically, FKBP5 appears to mediate gene–environment interactions through altered genetic and epigenetic regulation. For example, FKBP5 genes confer sensitivity to adverse early-life events (AELEs), and gene variants appear to contribute to MDD development (Matosin et al. 2018). FKBP5 function in MDD will be further discussed in this chapter.

In this chapter, we will discuss the neuroendocrine–immune interactions in MDD by describing the systems individually, how they interact, and the significant role of the GR in MDD.

6.2 Physiology of the Hypothalamic–Pituitary–Adrenal Axis

The HPA axis is a neuroendocrine unit which incorporates a range of interactions between the hypothalamus, the pituitary gland and the adrenal glands (Fig. 6.1). The axis begins with corticotropin-releasing hormone (CRH), a hypothalamic hormone produced in the paraventricular nucleus (PVN), regulated by stress (Brook and Marshall 2001). Release of CRH into the hypophyseal portal system results in binding to CRH receptors in the anterior pituitary, initiating the release of adrenocorticotropic hormone (ACTH) (Chalmers et al. 1995). In turn, this stimulates glucocorticoid (cortisol) synthesis in the adrenal cortex. Cortisol circulates in the bloodstream and has a range of metabolic effects. To maintain regulation of the HPA axis, cortisol acts in a negative feedback loop, preventing further release of CRH or ACTH (Fig. 6.1), thus aiding in maintaining basal homeostasis (Brook and Marshall 2001).

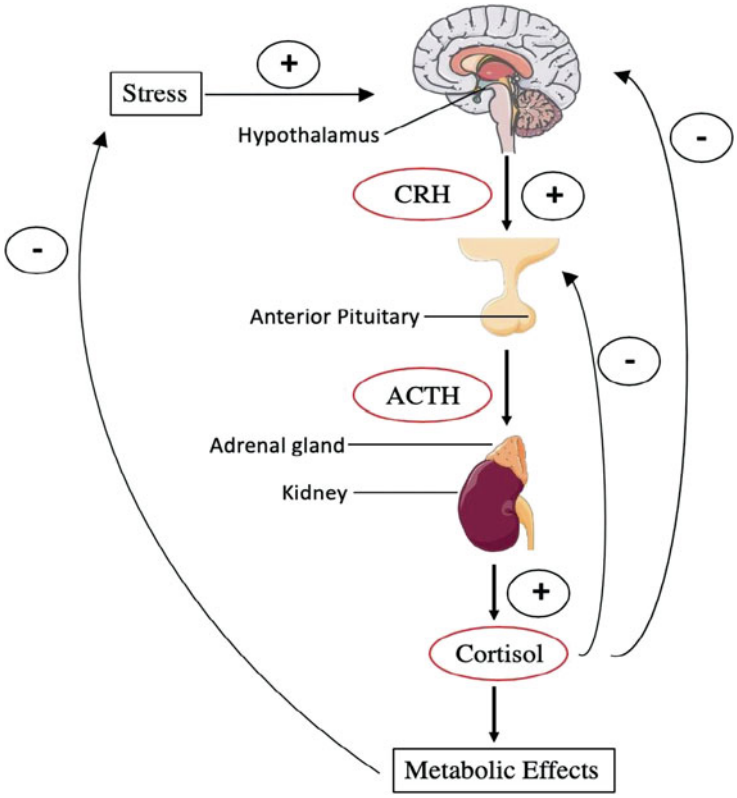

Fig. 6.1 The hypothalamic–pituitary–adrenal axis, representing the regulation of the production of cortisol from the adrenal cortex and of negative feedback regulation between the anterior pituitary and hypothalamus

This feedback regulation is mediated by cortisol binding to two cytoplasmic receptors: the lower affinity glucocorticoid receptor (GR) and higher affinity mineralocorticoid receptor (MR) (Arriza et al. 1988). Upon cortisol binding, the GR or MR will translocate to the nucleus and bind to glucocorticoid response elements (GREs), enhancing or suppressing gene transcription (Agler et al. 2007). Under normal conditions, MRs primarily help maintain cortisol levels, whilst under high stress conditions, GRs are progressively activated and bind cortisol to suppress the stress response (Kitchener et al. 2004). This GR activation inhibits CRH and ACTH expression, thus preventing HPA axis overactivation (Deng et al. 2015). However, if GR signalling is impaired, such as in chronic glucocorticoid stimulation, there will be a decrease in negative feedback on the hypothalamus and anterior pituitary, leading to increased glucocorticoid levels and dysregulation of the stress system. Reduced function of the GR is called glucocorticoid resistance, which can lead to HPA axis hyperactivity (Pariante and Lightman 2008). Therefore, normal GR

activation is crucial in restoring homeostasis of the stress response (Pariante and Miller 2001).

One of the strongest regulating factors for GR sensitivity is FKBP5 (Wochnik et al. 2005; Davies et al. 2002), a 51 kDa immunophilin protein (Kang et al. 2008). Binding of FKBP5 to the GR reduces GR-binding affinity for cortisol, and inhibits normal GR translocation to the cell nucleus, thereby preventing transcription (Wochnik et al. 2005). FKBP5 transcription is induced by GR activation, providing a short-loop negative feedback regulatory mechanism which controls GR sensitivity (Vermeer et al. 2003). Thus, FKBP5 is a negative regulator of glucocorticoid action, terminating secretion of cortisol and the stress response. Increased chronic expression of FKBP5 has been shown to cause glucocorticoid resistance; therefore, correct functioning of FKBP5 is crucial in maintaining HPA axis homeostasis (Denny et al. 2000).

6.3 Impaired Endocrine Regulation in MDD

Impaired GR signalling leads to altered negative feedback regulation and has frequently been reported in MDD. The combined dexamethasone/CRH (dex/CRH) test is commonly used to determine feedback control of the HPA axis, and involves pre-treating individuals with 1.5 mg of dexamethasone, followed by stimulation with 100 μg of CRH the subsequent day. Post-administration, blood samples are collected to measure plasma cortisol and ACTH to test for a dysfunctional response. For example, using the combined dex/CRH test, a significantly increased cortisol response has been observed in acutely depressed male and female patients when compared with controls (Holsboer et al. 1987; Modell et al. 1997; Kunugi et al. 2004). Furthermore, within the depressed patient cohort, those with a history of attempted suicide had a significantly higher ACTH and cortisol response than those without a suicide attempt (Kunugi et al. 2004). In healthy individuals, dexamethasone binds to the GR and activates feedback inhibition, in turn lowering cortisol secretion. However, in depressed patients, cortisol secretion does not appear to be inhibited. This suggests that GR-mediated negative feedback is impaired in MDD. Furthermore, salivary cortisol, measured in the morning or evening, is significantly higher in MDD patients compared with controls (Vreeburg et al. 2009; Veen et al. 2011; Sorgdrager et al. 2017). Therefore, a number of clinical studies have shown that MDD is associated with an impaired HPA axis response to stressors throughout the circadian rhythm. However, the relationship between HPA axis dysregulation and depression is complex, as not all MDD patients have an abnormal cortisol response to the dex/CRH test. For example, patients with chronic MDD have shown no difference in salivary or serum cortisol levels following the dex/CRH test when compared with matched controls (Watson et al. 2002; Carpenter et al. 2009). This therefore suggests a slightly different pathophysiology in patients experiencing HPA axis abnormalities compared to those that are not, which may become more evident as depression lasts or becomes worse and the clinical picture resembles treatment resistance. For example, in another series of studies, Juruena

and Pariante have shown that depressed patients show impaired feedback inhibition when challenged with dexamethasone, but normal response to prednisolone, a mixed GR and MR agonist, indicating a normal MR function (Juruena et al. 2006); however, severely depressed, treatment-resistant patients show impaired feedback inhibition even when challenged with prednisolone (Juruena et al. 2009, 2010, 2013).

HPA axis abnormalities have also been shown to influence and predict the development of MDD. When mean daytime cortisol was measured in patients at a mean age of 17.5 years, and upon follow-up at the age of 20, a previously high mean daytime cortisol level significantly predicted development of depression (Ellenbogen et al. 2011). Furthermore, an elevated cortisol response to the dex/CRH test in remitted patients has been correlated with a four-to-six-fold increased risk of relapse, compared to remitted patients with a normal cortisol response (Zobel et al. 2001). Similarly, a higher salivary cortisol response to low stress conditions in remitted MDD patients predicted a significant increase in depressive symptom score in the following 6 months (Morris et al. 2012). These studies suggest HPA axis abnormalities are closely related to the progression and long-term outcome of depression. As HPA dysregulation can precede a depressive episode, it suggests that abnormalities in the system arise prior to depression and may have a causal relationship.

A number of studies have shown differential HPA axis functioning between males and females (Kokras et al. 2019), suggesting that gender differences in MDD may be a variable that needs to be considered. This is particularly relevant, as following puberty girls are twice as likely to develop depression as adolescent boys (Salk et al. 2017). Additionally, depressed women have been found to have higher cortisol levels than depressed men, which is more prominent after a stressful or negative life event (Bangasser and Valentino 2014). Studies on rodents have shown that females have a larger stress-induced release of CRF, AVP, ACTH and cortisol compared to males, whilst negative feedback is also lower in females (Kokras et al. 2019). However, the directions of these changes are inconsistent between studies (Bangasser and Valentino 2014); thus, further research is required to understand the significance of these findings.

6.4 Activated Inflammatory Response in MDD

In addition to endocrine dysregulation seen in MDD, immune system alterations have also been associated with psychiatric disorders, with a well-established database of research linking immune system dysregulation with MDD. In fact, since the inflammation theory of depression was first introduced, a link between immune imbalance, depression and other psychiatric disorders has consistently been found (Stetler and Miller 2011; Pariante 2017). In a recent meta-analysis of 8887 depressed patients and matched controls, 58% of depressed patients had elevated serum C-reactive protein (CRP) levels (>1 mg/L), an acute-phase protein that rises in response to inflammation (Osimo et al. 2019). Additionally, a search of 11,813

depressed patients showed that 27% had low-grade inflammation (CRP >3 mg/L) (Osimo et al. 2019). In a similar meta-analysis of 5166 patients with depression, levels of CRP and inflammatory markers, such as interleukin (IL)-12, IL-6 and tumour necrosis factor (TNF)-α, were significantly higher in patients with depression than in controls (Osimo et al. 2020). These meta-analyses have been further corroborated by the UK Biobank study, the largest study to date including 26, 894 patients with depression and 59,001 controls (Pitharouli et al. 2021). Pitharouli et al. (2021) found significantly more patients with depression have CRP levels >3 mg/L when compared with controls. These results remained significant even after clinical and sociodemographic factors known to be associated with increased CRP, such as BMI, smoking, exposure to early-life adversity and low socio-economic circumstances, were adjusted for. Therefore, the aforementioned research demonstrates that increased circulating CRP is present in depression. Supporting this notion, studies have shown that both chronic and acute administration of pro-inflammatory challenges, such as interferon-alpha, produce a behavioural and emotional syndrome resembling depression (Nettis et al. 2020; Russell et al. 2019; Hepgul et al. 2016).

Additionally, in psychotropic-medication free MDD patients, plasma CRP is significantly correlated with inflammatory markers such as IL-6, TNF and soluble TNF receptor 2 (Felger et al. 2020). When comparing depressed patients with high versus low CRP (>3 mg/L vs. <3 mg/L), those with high CRP had a significant increase in these inflammatory markers, primarily driven by IL-6 and IL-1ra. Additionally, the cerebrospinal fluid concentrations of these cytokines in the high CRP group were also correlated with an increased Inventory of Depressive Symptomology Self Report (IDS-SR) score (Felger et al. 2020). Meta-analyses of cytokine-specific markers have found IL-1β, IL-6, TNF and CRP to be the most consistent biomarkers of inflammation in patients with MDD (Haapakoski et al. 2015).

Recent research has found evidence for differential relationships between inflammatory markers and different MDD symptoms, suggesting an 'inflammatory phenotype' of depression. For example, a higher polygenic risk score (PRS) for CRP has been associated with changes in appetite, fatigue and anhedonia, whilst a higher PRS for TNF-α is associated with fatigue (Kappelmann et al. 2021). Fried et al. (2019) similarly found CRP concentration to be associated with appetite and energy level whilst also reporting an association between IL-6, depression sum-score and 'aches and pains'. These findings suggest that specific inflammatory markers are associated with symptoms of depression, and thus may aid recruitment of patients with specific immune-related symptoms into clinical trials for immune-modulating drugs for MDD (Kappelmann et al. 2021). In terms of genetic regulation, it is also important to emphasise that the aforementioned study in the UK Biobank (Pitharouli et al. 2021) has found that the PRS for depression is associated with CRP levels, thus indicating a genetic contribution to inflammation, but only through metabolic and behavioural changes reflected by higher BMI and more frequent smoking behaviour in the patients, rather than a true immune-related genetic predisposition.

Interestingly, increased inflammatory markers in MDD patients have been associated with decreased treatment response, and therefore appear to predict antidepressant efficacy. For example, expression of mRNA for macrophage migration inhibitory factor and IL-1β in peripheral blood has been shown to predict decreased treatment response in MDD patients (Cattaneo et al. 2016). Additionally, increased BMI-corrected circulating CRP has been shown to be significantly elevated in treatment-resistant MDD patients (Chamberlain et al. 2019), whilst increased TNF-α, sTNF-R2 and IL-6 are associated with an increased number of failed treatments in MDD patients (Haroon et al. 2018). Furthermore, 6 mRNAs for P2RX7, IL-1β, IL-6, TNF-α, CXCL12 and GR have been found to differentiate treatment-resistant from treatment-responsive patients (Cattaneo et al. 2020). This research suggests MDD patients with pro-inflammatory biomarkers have a unique clinical profile that makes them more susceptible to treatment non-response, and thus may benefit from additional treatment strategies beyond first-line antidepressant regimes. It is also very interesting to note in this context that these authors find that resistance to antidepressants is associated with lower expression of GR mRNA together with high expression of pro-inflammatory mRNAs, thus supporting the notion that the increased inflammation in depression is associated with glucocorticoid resistance, at least as indicated by the low expression of GR (see below).

Considering this evidence, it is not surprising that conjunctive treatment of antidepressants with anti-inflammatories is a new treatment strategy currently in clinical trials, with the aim of targeting inflammation in those who exhibit increased concentrations of inflammatory biomarkers. This has recently successfully been shown with minocycline, an antibiotic that also has broad anti-inflammatory properties, and is able to penetrate the central nervous system through the blood–brain barrier (Nettis et al. 2021).

An additional consideration for research into inflammation in MDD is the impact of sex and sex hormones. For example, Moieni et al. (2015) administered endotoxin to both females and males to induce a pro-inflammatory cytokine response—increased IL-6 and TNF-a. Following endotoxin administration, females reported a significantly greater increase in depressed mood and social disconnectedness than males, suggesting females may be more susceptible to the effects of inflammation. Additionally, immune cells have sex hormone receptors, and thus respond directly to changes in sex hormone levels (Brundin et al. 2021). For example, two estrogen receptors (ER), ER-alpha and G-protein ER1, are associated with anti-inflammatory phenotypes, and expressed on human primary monocytes in peripheral blood. ER-alpha acts to inhibit IL-6 expression through NF-κB transcriptional inhibition, whilst G-protein ER1 is a vital co-regulator of ER-alpha and its aforementioned actions (Pelekanou et al. 2016). In addition, microglial cells contain estrogen receptors, and estrogens have an inhibitory effect on neuroinflammatory activity (Villa et al. 2016).

Studies have also shown fluctuating estradiol across the menstrual cycle impacts mood and neurological response to psychosocial stress (Albert et al. 2015), whilst during the different phases of the menstrual cycle, and thus times of hormone fluctuation, expression patterns of immune response genes differ (Brundin et al.

2021). For example, during the late luteal phase of the menstrual cycle, when estrogen levels are decreasing, high levels (>3 mg/L) of the inflammatory biomarker CRP are reported in women (Gold et al. 2016; Harding and Headon 2022). Furthermore, high CRP levels are significantly positively associated with premenstrual mood changes (Gold et al. 2016). Thus, the research discussed above suggests that hormone level fluctuations impact both the immune system and susceptibility to stress, and thus could influence the inflammatory component of depression.

6.5 Neuroendocrine–Immune System Interaction

A relationship between the two systems discussed above—neuroendocrine and immune—has also been extensively reported, with neuroendocrine–immune interactions impacting both the immune response and hormonal functioning to maintain homeostasis (Ashley and Demas 2017). Along with bidirectional crosstalk between the systems, neuroendocrine cells can also produce cytokines whilst immune cells produce low concentrations of hormones (Verburg-van Kemenade et al. 2017). Notably, HPA axis hyperactivity and increased inflammation are the two most consistently described pathophysiological findings in major depression (Pariante 2017). Thus, the contribution of the immune system and the consequent inflammation are important factors to consider when discussing neuroendocrine interactions with mood disorders.

As discussed, the HPA axis has been at the centre of the neuroendocrine–immune relationship with mood disorders, particularly in patients with more severe, treatment-resistant depression. A number of human and animal studies have provided evidence that the underlying physiological mechanisms of inflammation lie in stress-related pathways. In terms of stress-related pathways, it should be noted that so far, this chapter has mostly dealt with psychological stress. These pathways lead to increased circulating levels of monocytes and neutrophils, alongside activation of the HPA axis and thus increased cortisol levels. For example, following activation, immune cells such as monocytes are trafficked to the brain vasculature, triggering subsequent inflammatory signalling (Miller and Raison 2016). Multiple pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 act as activators of the HPA axis, whilst immune cells express both GR and adrenergic receptors (Ménard et al. 2017). Conversely, cortisol and corticosterone are potent anti-inflammatory steroid hormones and can regulate the expression of cytokines, adhesion molecules and chemoattractants (Eskandari et al. 2003). Therefore, the HPA axis is a central control centre for the inflammatory responses, both in the central nervous system and throughout the body (Otmishi et al. 2008).

Persistent HPA axis hyperactivation, such as that seen in some MDD patients, can lead to chronic glucocorticoid resistance. As the GR physiologically mediates HPA axis negative feedback, glucocorticoid resistance leads to both HPA axis hyperactivity and a decrease in GR-mediated anti-inflammatory action, and thus increased inflammatory markers (Pariante 2017). Lastly, the role of the kynurenine pathway, an alternate metabolic pathway for tryptophan degradation, is worth mentioning.

This pathway is frequently activated in both inflammation and depression (Sforzini et al. 2019; Savitz 2020), and may also be activated by an excess of cortisol (Menke 2019). These data suggest a potential role for the kynurenine pathway as a biological mechanism involved in neuroendocrine–immune interactions in MDD.

As discussed previously, sex differences have been seen in both the immune and endocrine systems; however, there is a limited body of research on neuroendocrine–immune crosstalk and sex. We will give only a brief summary, as an in-depth discussion is beyond the scope of this chapter (see Chap. 10). In a recent review, some sex differences in the medial preoptic area were suggested to involve endocrine–immune crosstalk (Arambula and McCarthy 2020). For example, Lenz et al. (2018) found a greater and more active number of mast cells in the medial preoptic area of male neonates than females, and these mast cells mediate some aspects of brain sexual differentiation. Therefore, it has been hypothesised that imbalances or changes to the endocrine–immune system may impact sex differences in the medial preoptic area, and thus differences in neurodevelopment (Arambula and McCarthy 2020). There have been no studies to date to confirm the above hypotheses; however, these suggestions may contribute to understanding sex differences in neuropsychiatric and neurodevelopmental conditions.

6.6 Neuroendocrine–Immune Models

6.6.1 The 'Glucocorticoid Resistance Model'

This coexistence of increased inflammation and HPA axis dysfunction in MDD has led to a debate regarding cause and effect: is HPA axis hyperactivity causing inflammation or *vice versa*? As the GR mediates negative feedback on the HPA axis, dysfunction of the GR leads to impaired HPA axis negative feedback and thus increased glucocorticoid levels. Increased glucocorticoids are known to inhibit immune function, as previously discussed; however, in depression high concentrations of pro-inflammatory cytokines co-exist with high levels of glucocorticoids (Zunszain et al. 2011). Since the 1990s, the 'glucocorticoid resistance model' has been the accepted explanation for this concurrence, due to the potential immune activating features of glucocorticoids in MDD (Munhoz et al. 2010). This model suggested a reduced function of the GR; thus the glucocorticoid resistance seen in some MDD patients allows pro-inflammatory pathways to evade normal feedback inhibition by glucocorticoids (Pariante 2017). The increased immune response is due to immune cells becoming resistant to the anti-inflammatory role of cortisol; thus, even if these patients have higher cortisol levels, there is less inhibition of inflammation. Therefore, according to the 'glucocorticoid resistance model', the increased HPA axis activation and consequential hypercortisolaemia are suggested to be the cause of the increased inflammatory response in depression, rather than a result of glucocorticoid resistance. Using models of depression-induced inflammation, recent research has confirmed the finding that glucocorticoids can potentiate pro-inflammatory processes (Horowitz et al. 2020). Studies showing a

concomitant increase in inflammatory biomarkers and reduced GR expression or function support this model (Nikkheslat et al. 2015; Cattaneo et al. 2012, 2020; Mariani et al. 2021). However, in a recent meta-analysis testing the association between glucocorticoid resistance and increased inflammation in MDD, the original findings from the 'glucocorticoid resistance model' have not been upheld, and are thus being questioned (Perrin et al. 2019).

Perrin et al. (2019) analysed all 32 studies that have looked at both HPA axis and inflammation data in the same MDD patients (2087 patients), a surprisingly small number compared to the studies which have looked at one or the other factor. Combining the studies that reported dexamethasone suppression test results with those that recorded GR expression, or *in vitro* assays of GR function to quantify glucocorticoid resistance, the meta-analyses found limited evidence for a positive association between glucocorticoid resistance and inflammation. Therefore, despite being limited by the small number of studies, the analyses indicate that the 'glucocorticoid resistance model' may not be the only explanation for the complex relationship between glucocorticoid resistance and immune system escape and suggests a need for further research (Perrin et al. 2019). Additionally, despite the presence of increased inflammatory biomarkers (IL-6, TNF-alpha and MIF) and reduced GR mRNA expression in the 190 MDD patients analysed, the BIODEP study similarly found no clear evidence for a correlation between inflammatory biomarkers, GR mRNA expression and salivary cortisol levels (Cattaneo et al. 2020). Therefore, this research suggests that GR mRNA expression does not fully elucidate the mechanism behind increased inflammation in MDD.

Moreover, in recent research on rodents, different forms of stress resulted in different HPA axis function and inflammatory outcomes (Du Preez et al. 2020). For example, physical stress related to repeated injections induced increased corticosterone reactivity and decreased plasma TNF-α and IL-4, whilst the psychosocial stress of social isolation induced increased TNF-α and decreased corticosterone reactivity. Despite the presence of a depressive-like phenotype, neither circumstance found increased HPA axis activity and increased inflammatory biomarkers, which would have been expected in the 'glucocorticoid resistance model'. Therefore, if glucocorticoid resistance is not the cause of increased inflammation in depression, additional hypotheses are required to explain the relationship between high cortisol levels and inflammation in MDD.

6.6.2 The 'Pro-inflammatory Cortisol' Model as an Alternative to the Glucocorticoid Resistance Model

Despite the prominent anti-inflammatory effects of glucocorticoids, research over the years has indicated that during stress glucocorticoids may also have pro-inflammatory properties. Glucocorticoid secretion activated by chronic stress has been shown to increase NF-κB activation in the frontal cortex and hippocampus of rodents whilst also increasing pro-inflammatory gene expression, thus suggesting a pro-inflammatory role for glucocorticoids (Munhoz et al. 2010). NF-κB is a

mediator of inflammatory responses, inducing expression of pro-inflammatory genes and regulating the survival of both innate immune cells and T cells; thus, increased levels result in a pro-inflammatory response (Liu et al. 2017). Additionally, when corticosterone signalling in mice is inhibited with metyrapone, a glucocorticoid synthesis inhibitor, inflammation decreased despite the introduction of social stress (Niraula et al. 2018).

Consistent with animal studies, research in humans has found that pre-treatment with hydrocortisone in healthy participants induces a systemic inflammatory response following high cortisol concentrations (Yeager et al. 2011). Yeager et al. (2016) later found that administration of cortisol, to concentrations which mimic those seen during systemic stress, induces an upregulation of monocytes, macrophages and neutrophils, and thus a pro-inflammatory response in participants (Yeager et al. 2016). Most recently, *in vitro* studies of human hippocampal progenitor cells have shown that administration of dexamethasone prior to an immune challenge enhances inflammatory effects in these neural cells and upregulates multiple innate immune genes (Horowitz et al. 2020). These effects were most potent when the hippocampal cells were exposed to cortisol 24 hours prior to immune challenge. Therefore, this research provides evidence for an alternative to the 'glucocorticoid resistance model', which proposes cortisol as a pro-inflammatory mediator of stress reactions, and thus potentially another mechanism for the coexistence of inflammation and HPA axis dysfunction in MDD. As this model has not been tested in MDD, further research is required for the application of the 'pro-inflammatory cortisol' model.

6.7 HPA Axis Dysregulation in MDD: The Role of FKBP5

6.7.1 FKBP in MDD

Research into the neuroendocrine-immune relationship would not be complete without analysing the role of the GR in HPA axis dysregulation in MDD. In fact, research into this pathophysiology has identified FKBP5, a regulator of GR sensitivity, as a potential molecular target at the HPA axis interface. In humans, single nucleotide polymorphisms (SNPs) in FKBP5 are associated with differential FKBP5 mRNA expression, leading to changes in GR sensitivity, and in turn HPA axis regulation (Binder et al. 2004). Due to the role of FKBP5 in HPA axis function, and the established link between HPA axis dysfunction and MDD, several studies investigated the relationship between FKBP5 and MDD (Klengel and Binder 2015).

When MDD patients were compared with healthy controls, FKBP5 SNPs (rs1360780, rs3800373, rs4713916, rs9296158, rs9394309, rs9470080) were found to be significantly associated with MDD status (Lekman et al. 2008; Szczepankiewicz et al. 2014) and with an increased recurrence of depressive episodes (Binder et al. 2004). Additionally, significantly higher FKBP5 mRNA levels in leukocytes have been reported in MDD patients, compared with controls (Cattaneo et al. 2012), and are seen *post-mortem* in both the hippocampus (Mamdani

et al. 2015) and cortical regions of the brain (Tatro et al. 2009). This research provides evidence that certain FKBP5 SNP alleles are more frequent in MDD patients than controls and are associated with MDD risk. Thus, this suggests FKBP5 polymorphisms cause a baseline difference in GR sensitivity, increasing GR resistance and decreasing efficiency of negative feedback on the HPA axis, thereby increasing MDD risk. Some studies also show evidence of an effect of FKBP5 polymorphisms on response to antidepressants (Stamm et al. 2016; Fabbri et al. 2018). These variations may explain why HPA axis dysregulation has been seen prior to a depressive episode and can predict development of depressive symptoms or possibly the likelihood of response to antidepressants.

6.7.2 FKBP5: Gene–Environment Interactions

The strongest evidence for gene–environment interaction between glucocorticoid-related genes and a stressful environment is not offered by the GR or the MR but by FKBP5, and we are therefore discussing this more in depth. As with genetic variables, environmental stressors are also a major cause for the development of MDD. Adverse early-life events (AELEs) have been identified as a major environmental cause for the development of MDD (Kendler et al. 1999). Interestingly, AELEs have also been shown to impact HPA axis functioning (Mangold et al. 2010; Shapero et al. 2014), and FKBP5 has been identified as a key target (Klengel et al. 2013).

The relationship between different gene–environment interactions has been shown in a study evaluating FKBP5 polymorphisms (rs3800373, rs9296158, rs1360780, rs9470080) in preschool children (Scheuer et al. 2016). Minor allele carriers of the SNPs had significantly increased risk of developing MDD if exposed to adverse life events, compared with homozygous carriers of the major allele (Scheuer et al. 2016). It should be noted that a significantly increased risk of MDD was only seen in those exposed to mild-to-moderate adverse events, rather than severe. Further research corroborated these findings, comparing 148 adolescent patients with MDD to 143 typically developing controls (Piechaczek et al. 2019). Participants who had reported a higher number of early-life stressors (using the Munich Event List and modified Life Event Survey) and were also carriers of FKBP5 SNPs (rs3800373, rs1360780) had increased risk for being in the MDD group (Piechaczek et al. 2019). The researchers also showed that adolescent carriers of FKBP5 SNPs (rs3800373, rs9296158, rs9470080) who had experienced sociodemographic stressors, such as unemployment or migrant background of parents and lower secondary education of the participant, had an increased risk of MDD. This shows significant interactions between these SNPs and stress in predicting depression in adolescents. Kang et al. (2020) also reported significant interaction effects between childhood physical abuse and FKBP5 SNPs (rs3800373, rs1360780, rs4713916). Those carrying the minor alleles of the SNPs showed higher depression scores than non-carriers when exposed to abuse. Importantly, these SNPs alone had no significant effect on depression risk or symptoms, as exposure to

early-life stress was vital for an increased risk of depression (Piechaczek et al. 2019; Kang et al. 2020). Therefore, the minor alleles of the FKBP5 polymorphisms act as risk alleles, increasing susceptibility to the pathogenic effects of childhood abuse in developing childhood and adolescent depression.

The research discussed provides evidence that genetic variation in FKBP5 impacts the risk of MDD by altering an individual's sensitivity to the effects of AELEs. Thus, genetically driven variability produces individual differences in the risk of MDD, and may explain why only some individuals who experience AELEs develop MDD. Importantly, whilst SNPs may act as a risk factor for MDD, these studies have shown that SNP interaction with AELEs is crucial in mediating significant risk of depression. Although previous studies discussed showed a relationship between FKBP5 and MDD, life history was not taken into account (Binder et al. 2004; Lekman et al. 2008; Tatro et al. 2009; Cattaneo et al. 2012; Szczepankiewicz et al. 2014; Mamdani et al. 2015). Therefore, it is possible that the cohort of patients used had in fact experienced early-life adverse events, which would explain the significant relationship observed between FKBP5 SNPs and MDD.

FKBP5 SNPs that interact with early-life adverse events are associated with increased FKBP5 mRNA expression, leading to changes in GR sensitivity and, in turn, HPA axis regulation (Binder et al. 2004). Reporter gene assays of SNPs rs1360780, rs9296158, rs9470080a and rs3800373 found that rs1360780 was situated closest to the GRE, which transcriptionally regulates FKPB5 (Klengel et al. 2013). The homozygous risk allele (AA), but not the protective (GG) genotype of rs1360780, was shown to mediate the interaction of intron 7 with the FKBP5 transcription start site via three-dimensional loop formation. AA also mediated intron 2 in a genotype-dependent interaction, again with the FKBP5 transcription start site. Consequently, this leads to enhanced FKBP5 gene transcription in response to GR (Klengel et al. 2013). FKBP5 response therefore differs between risk allele and protective allele carriers. The response caused by increased FKPB5 transcription is consistent with previous research that showed a genetic predisposition in FKBP5 can lead to a stronger cortisol reaction to stressors, and glucocorticoid resistance in healthy controls (Ising et al. 2008; Binder et al. 2008).

6.7.3 FKBP5: Epigenetic Mechanisms

As for gene–environment interaction, and even if some studies have shown some evidence of epigenetic regulation of the GR in response to stress (Witzmann et al. 2012; Mourtzi et al. 2021), the strongest evidence for epigenetic mechanisms operating in the regulation of glucocorticoid function comes from studies on FKBP5. Growing evidence suggests that epigenetic alterations are a key component by which environmental stressors interact with the genome, increasing the risk of depressive symptomology (Davies et al. 2019). It has been suggested that FKBP5 epigenetic and environmental mechanisms play a role in the pathophysiology of

HPA axis dysregulation, whereby FKBP5 epigenetic components bridge the genetic and environmental association and contribute to MDD pathophysiology (Lin and Tsai 2019). There has been a particular focus on AELEs, as adverse events in adulthood have not found a significant association with outcome (Lahti et al. 2016; Cristóbal-Narváez et al. 2017).

Early-life adverse events have been shown to impact allele-specific epigenetic modification of FKBP5. Epigenetics refers to the potentially heritable, though environmentally modifiable, regulation of gene expression and function mediated through non-DNA-encoded mechanisms (Sun et al. 2013). For example, common epigenetic modifications in MDD include histone acetylation and DNA methylation (Sun et al. 2013). Whilst the exact molecular epigenetic mechanisms behind the FKBP5 gene–environment interactions in MDD are not entirely clear, recent research has elucidated a few potential mechanisms.

Patients with the rs1360780 risk allele of FKBP5 who also experienced childhood abuse had significantly decreased DNA methylation in intron 7, compared with controls or protective genotype carriers (Klengel et al. 2013). Furthermore, greater childhood exposure to trauma correlated with a greater decrease in methylation. Multiple studies have further confirmed decreased intron 7 DNA methylation in MDD patients, and healthy carriers of the high-risk allele exposed to AELEs (Non et al. 2016; Tozzi et al. 2018; Klinger-König et al. 2019). Therefore, individuals with the high-risk FKBP5 allele appear to be more susceptible to epigenetic changes following childhood abuse.

In addition, this decrease in FKBP5 CpG methylation in patients with early-life stress and depressive phenotypes has been found to upregulate FKBP5 in peripheral blood. Importantly, this upregulation of FKBP5 in peripheral blood promoted NF-kB signalling in immune cells and showed positive correlation with pro-inflammatory genes such as interleukin and toll-like receptors (Zannas et al. 2019).

Therefore, these findings suggest that AELEs may chronically influence both the HPA axis and inflammatory regulation through epigenetic modification of the FKBP5 gene. As GR mediates the negative feedback response of the HPA axis, impaired function can lead to long-term HPA axis dysregulation. This may explain why certain patients—those with high-risk alleles—have a higher risk of MDD. Thus, this research shows how a genetic predisposition to react more strongly to environmental stress interacts with AELEs, and may increase the risk of MDD.

6.8 Conclusion

MDD is significantly linked to physiological modifications in our body, most notably neuroendocrine–immune interactions. Whilst research has shown there is a neuroendocrine and immune system interplay in MDD, our understanding of the exact mechanism is still limited. The ‘glucocorticoid resistance model’ provided the first possible explanation; however, it is clear that further modifications to this model are required following the discovery of the pro-inflammatory role of cortisol.

Therefore, whilst this research has further elucidated neuroendocrine–immune mechanisms in MDD, additional research in humans is still necessary to overcome the uncertainties that remain, and thus help us to understand the biological mechanism underpinning MDD. Research into GR dysfunction in MDD has found FKBP5, a key regulator in GR function, to be a potential biomarker for MDD, specifically in those with AELEs.

6.9 Key References

Binder et al. 2004: this was the first paper to find an association between FKBP5 polymorphisms, HPA axis dysregulation and increased susceptibility for depression.

Cattaneo et al. 2020: this research found six mRNAs, all associated with the immune response, differentiated treatment-resistant from treatment-responsive patients with depression.

Pariante and Miller 2001: the first review of the literature on the associations between depression, glucocorticoid resistance and the impact of antidepressants on the glucocorticoid receptor.

Pitharouli et al. 2021: this is the largest study to date demonstrating that increased CRP, and thus inflammation, is associated with depression.

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