Published in final edited form as:
Curr Opin Endocr Metab Res. 2022 June ; 24: 100356. doi:10.1016/j.coemr.2022.100356.

Cause or consequence? Understanding the role of cortisol in the increased inflammation observed in depression

Nare Amasi-Hartoonian[1], **Luca Sforzini**[1], **Annamaria Cattaneo**[2,3], **Carmine Maria Pariante**[1,4]

[1]Institute of Psychiatry, Psychology and Neuroscience, King's College London, Department of Psychological Medicine, London, UK

[2]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

[3]Laboratory of Biological Psychiatry, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

[4]National Institute for Health and Research Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, UK

Abstract

Glucocorticoids such as cortisol are a class of steroid hormones that play an important role in co-ordinating the body's response to stress. Elevated cortisol levels and increased inflammation have frequently been reported in patients with depression. The currently accepted "glucocorticoid resistance" model posits this increased inflammation as a consequence of reduced sensitivity to cortisol's putative anti-inflammatory action. However, opposing evidence has accumulated that supports a more recent model, which instead proposes that cortisol possesses immune potentiating properties and may thus directly cause the increased inflammation seen in depression. Despite all of this, a clear explanation of the neuroendocrine mechanism that contributes to the development of depression is still lacking and thus requires further investigation in improved future studies.

Keywords

Hypothalamic-pituitary-adrenal axis; inflammation; major depressive disorder; glucocorticoid resistance; cortisol; glucocorticoid receptor

2 Introduction

Increased inflammation and hypothalamic-pituitary-adrenal (HPA) axis alterations have been consistently associated with depression, or at least with a subgroup of individuals with depression (Pariante, 2017). It is widely known that the HPA axis is strictly implicated in inflammation. Its activation triggers the release of glucocorticoids, mainly cortisol in humans, which plays a crucial role in anti-inflammatory and immunosuppressive processes

Correspondence to: Nare Amasi-Hartoonian.
Corresponding author: nare.amasi-hartoonian@kcl.ac.uk.

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

(Bellavance & Rivest, 2014). However, the clear relationships between the HPA axis and inflammation and depression and with one another have yet to be fully elucidated.

Initial findings regarding the neuroendocrine and biological correlates of major depressive disorder (MDD) consistently identified HPA axis hyperactivity and subsequent increased cortisol levels, which have also been observed in patients with treatment-resistant depression that is associated with greater severity. As a result, the “glucocorticoid resistance” theory emerged in the late 90s, which proposes that the glucocorticoid receptor (GR) is less sensitive to cortisol and does not bind as effectively, thus the regulation of the HPA axis through negative feedback inhibition becomes impaired, resulting in continued activation and production of the axis components (Pariante & Miller, 2001; Pariante & Lightman, 2008; Anacker et al., 2011). This diminished sensitivity of the GR is considered to be due to reduced GR function and expression that has been reported in depression by a large number of experimental, biological and molecular studies.

During the last 10 years, evidence started to accumulate not only from animal studies showing that repeat social defeat (a form of chronic stress) can induce glucocorticoid-resistant monocytes, enhanced neuroinflammatory signalling and depressive-like behaviours in animal models (Weber et al., 2017), but also from human studies that noted the coexistence of reduced GR function/expression or HPA axis hyperactivity and elevated inflammation in depressed patients (Pariante, 2017). Therefore, scientists naturally inferred that this single molecular mechanism of glucocorticoid resistance is the common factor that is related to both HPA axis function and immune activation. That is to say, immune cells, which express GR (Ménard et al., 2017), become less sensitive to cortisol’s ‘physiological anti-inflammatory’ action that may lead to the escape and hyperactivity of monocytes (and other immune cells), thus explaining the resulting increased inflammation that is observed. But despite all of this, the evidence is conflicting, as studies have reported findings that are in disagreement with the current or simplest version of the glucocorticoid resistance model.

3 Inflammation, HPA axis and glucocorticoids in MDD

Results from recent meta-analyses (Osimo et al., 2020; Osimo et al., 2019) and case-control studies (Chamberlain et al., 2019; Lynall et al., 2020; Cattaneo et al., 2020) have confirmed the presence of increased inflammation in depression, particularly in treatment-resistant patients, through elevated levels of inflammatory markers like the C-reactive protein and higher immune cell counts compared with healthy controls, even in treatment-responsive patients. Most importantly, the largest study to have corroborated this finding utilised data on approximately 27 thousand people with MDD from the UK Biobank and suggested the existence of a core biological association between depression and increased inflammation, since this association remains significant after adjusting for clinical and psychosocial confounding factors (Pitharouli et al., 2021). Several human and animal studies have shown that this association is most likely due to stress system activation, leading to the release of pro-inflammatory cytokines and activated immune cells like monocytes, which occur along with HPA axis hyperactivity and increased cortisol levels (Raison et al., 2006; Miller & Raison, 2016; Raison & Miller, 2003). Moreover, associations were found between specific inflammatory markers and different MDD symptoms (Kappelmann et al., 2021; Fried et al.,

2020; Felger et al., 2020), and individuals exposed to interferon-α, a pro-inflammatory trigger, displayed depressive-like symptoms (Nettis et al., 2020; Russell et al., 2019). Hence, clinical trials have investigated the putative therapeutic benefits of anti-inflammatory treatment in inflamed MDD/depressed patients with promising results (Nettis et al., 2021; Ménard et al., 2017).

However in the 2000s, evidence opposing the glucocorticoid resistance model began to surface. For example, Munhoz and colleagues (2006) reported that, contrary to the anti-inflammatory effects of glucocorticoids via NF-κB inhibition, rats exposed to chronic unpredictable stress had elevated glucocorticoid levels, which resulted in increased NF-κB activation and pro-inflammatory gene expression induced by exposure to acute stress. Furthermore, pre-treatment with a GR antagonist weakened this effect, thus suggesting the putative immune potentiating properties of glucocorticoids. This pro-inflammatory action has also been observed in work conducted in our lab in human hippocampal progenitor cells that were treated with glucocorticoids prior to an inflammatory stimulus (Horowitz et al., 2020).

Moreover, investigating the biological outcomes of different types of stress in male mice failed to yield a consistent finding of HPA axis hyperactivity and increased inflammation, as researchers in our lab found that physical stress leads to hypercortisolaemia and reduced pro-inflammatory cytokine levels, while psychosocial stress leads to hypocortisolaemia and elevated pro-inflammatory cytokine levels (Du Preez et al., 2020). Furthermore, again in our lab, Perrin and colleagues (2019) failed to identify a strong positive correlation between glucocorticoid resistance and inflammation in their meta-analysis of studies examining both cytokine levels in depressed patients and measures of glucocorticoid resistance, including plasma cortisol levels, dexamethasone (synthetic glucocorticoid) suppression test, *GR* expression and *in vitro* assays of GR function. Similarly, Cattaneo et al. (2020) did not report a clear correlation between serum CRP inflammatory marker levels and glucocorticoid-related gene expression.

Therefore, this recent information has led the scientific community to postulate that the inflammation seen in depression may not solely be a *consequence* of glucocorticoid resistance and reduced GR signal but rather could be *caused* by the potential pro-inflammatory action of cortisol whose levels are aberrantly increased due to HPA axis hyperactivity.

4 The two models

The **“glucocorticoid resistance” model** was first proposed in the 1990s in the context of inflammatory diseases like asthma and inflammatory bowel disorders (Lamberts, 1996), and later became an established finding in psychiatry in the 2000s (Raison & Miller, 2003; Pariante & Miller, 2001). This phenomenon is the current consensus theory for HPA axis hyperactivity and the accompanied increased inflammation that are observed in depression. On the basis of this model, the **physiological anti-inflammatory action** of cortisol in humans increases as its concentration rises, that can range from *physiological levels* (during the day), to *stress levels* (those seen in depressed patients or that is induced

experimentally) and to *pharmacological levels* (that is achieved with a large hydrocortisone or comparable synthetic glucocorticoid administration). A visual representation of this model is depicted in Figure 1 where despite the higher cortisol levels in depressed patients (**straight line**) compared to healthy controls (**dotted line**), their immune cells are resistant to cortisol's aforementioned anti-inflammatory action, thus inflammation is less inhibited in these individuals at different concentrations of cortisol than controls, hence resulting in the increased inflammation that is seen in depression. The scientific literature investigating this resistance to cortisol points to abnormalities involving the GR, which under normal conditions has a low affinity for cortisol and therefore requires high glucocorticoid concentrations to be fully activated (Anacker et al., 2011). Reviews and primary research have reported reduced function and/or expression of the GR in the immune cells of depressed patients, particularly those that are inflamed (Pariante & Miller, 2001; Anacker et al., 2011; Pariante & Lightman, 2008; Mariani et al., 2021; Cattaneo et al., 2020; Cattaneo 2013). This is considered to be influenced by gene-environment interactions at *FKBP5*, a negative regulator of GR function, whereby early life adversity (even *in utero*) and *FKBP5* risk alleles can lead to or exacerbate epigenetic alterations in this gene, thus increasing MDD risk (Mourtzi et al., 2021; Lin and Tsai, 2019; Matosin et al., 2018) and potentially promoting NF-κB-driven peripheral inflammation (Zannas et al., 2019). Other evidence supporting this model includes the reports of glucocorticoid resistance, inflammation and depressive-like behaviours in the aforementioned repeated social defeat animal models of depression (Weber et al., 2017) and a study showing that administration of dexamethasone (a synthetic glucocorticoid and GR agonist) leads to reduced GR target gene expression in patients with depressive disorders and mouse models (Arloth et al., 2015).

However, despite the existing findings in favour of this model, the previously mentioned meta-analysis only reported modest support for the association between glucocorticoid resistance and cytokine-mediated inflammation in depressed patients compared to controls (Perrin et al., 2019). In addition, the authors noted not only the limited number of included articles and study subjects for which information on both glucocorticoid resistance and inflammation was collected, but also that most individual studies had utilised only a single method to quantify glucocorticoid resistance.

The accumulation of more recent evidence against the current model has resulted in a conceptual shift; providing an alternative explanation to the notions outlined in the first review published on the relevance of glucocorticoid resistance in depression (Pariante & Miller, 2001). This newer **"pro-inflammatory cortisol" model** that has emerged, proposes the idea that glucocorticoids may possess **pro-inflammatory properties** during stress, and so the high cortisol levels, typically observed in depressed patients, may be the *cause* of the elevated inflammation in MDD, instead of just a *consequence* of glucocorticoid resistance. This phenomenon is supported by findings from animal research demonstrating that increased concentrations of corticosterone (the primary glucocorticoid in rodents) induced by chronic unpredictable stress or achieved through glucocorticoid administration/manipulation resulted in enhanced inflammation in response to acute stress (Munhoz et al., 2006, 2010). Furthermore, Niraula and colleagues (2018) found that administration of metyrapone (a glucocorticoid synthesis inhibitor) and surgical removal of the adrenal

glands (where glucocorticoids are synthesised) to inhibit corticosterone production, led to the prevention of neuroinflammatory signalling and inflammatory monocyte release into circulation when exposed to repeated social defeat stress, indicating that corticosterone increases inflammation in this model. In healthy human subjects, exposure to stress-associated concentrations of cortisol for 6 hours via hydrocortisone (intravenous cortisol) administration, elicited a pro-inflammatory response, including a significant increase in IL-6 cytokine levels, following an inflammatory stimulus (Yeager et al., 2016, 2011). Similar findings were reported by Horowitz et al. (2020) in our lab, who investigated the effect of dexamethasone or cortisol treatment in human hippocampal progenitor cells prior to an inflammatory stimulus, which resulted in the increased expression of several innate immune genes. Moreover, these studies interestingly observed that this pro-inflammatory effect was maximal at intermediate (stress-relevant) cortisol levels, but not at high (pharmacological) or low (physiological) concentrations, and when there was a delay or rest period of 24 hours before the inflammatory stimulus. This model has not yet been tested in human patients with depression. As displayed in Figure 2, this alternative model postulates that cortisol possesses a pro-inflammatory action and so the elevated stress-levels of this hormone that are found in depressed patients (**straight line**) compared to healthy controls (**dotted line**) is in fact the reason for the increased inflammation that is present in these individuals, and not just merely resulting from glucocorticoid resistance.

5 Epigenetics and cell/tissue type

The role of epigenetic mechanisms has been well investigated in relation to the "glucocorticoid resistance" model, with several studies reporting the link between early life adversity/trauma, depression or stress-related conditions and the hypomethylation of the aforementioned *FKBP5* gene or hypermethylation of the *NR3C1* (GR) gene promoter, which leads to decreased GR activity or decreased GR mRNA and protein expression (Mourtzi et al., 2021; Farrell and O'Keane, 2016; Spies et al., 2021). This reduced *FKBP5* methylation was also associated with promoting inflammation (Palma-Gudiel et al., 2021; Zannas et al., 2019), although more studies including this measure are required, as well as further research to clarify inconsistent findings (Lin and Tsai, 2019; Farrell and O'Keane, 2016). Moreover, animal and cell culture studies found that histone deacetylation correlated with reduced transcription factor binding to the GR promoter and depressive behaviours (Farrell and O'Keane, 2016), in addition to miRNA overexpression resulting in GR downregulation (Jung et al. 2015; Vreugdenhil et al., 2009).

The contribution of epigenetics within the context of the "pro-inflammatory cortisol" model has not yet been explored. However, it is known that the GR interacts with coactivators that possess histone acetyltransferase activity to regulate immune gene expression and the suggested mechanisms for the immune-potentiating effects of glucocorticoids involves inducing the expression of genes with a pro-inflammatory function like *TLR2*, partly through GR interaction with NF-κB response elements (Liberman et al., 2018; Desmet & De Bosscher, 2017; Xavier et al., 2016).

It is also considered that glucocorticoids can exert contrasting actions depending on the cell or tissue type, with pro-inflammatory effects reportedly demonstrated in dendritic cells

Europe PMC Funders Author Manuscripts

or the brain and anti-inflammatory effects in peripheral immune cells like neutrophils (Liberman et al., 2018; Xavier et al., 2016). Although, both of these effects have been observed within the same cell type (Cruz-Topete & Cidlowski, 2015; Xavier et al., 2016).

6 Future directions

In spite of this rationale, it is important to note that the interplay between the endocrine and immune systems is complex and paradoxical (Perrin et al., 2019), since cortisol is not only implicated in increasing inflammation, but it can also bind the GR and repress the expression of genes encoding pro-inflammatory cytokines (Anacker et al., 2011). Moreover, this relationship is bidirectional as pro-inflammatory cytokines themselves can inhibit GR function (Pariante et al., 1999) through activation of mitogen-activated protein kinases like p38 (Pariante & Lightman, 2008) and JNK (Zhang et al., 2020) thus in turn contributing to glucocorticoid resistance resulting in a feed-forward inflammatory cascade (Raison & Miller, 2003).

A potential explanation of cortisol's biphasic effects on the immune system (that seem to be not only time- and dose-dependent but also reliant on the GR) may be that stress-concentrations of glucocorticoids prime the innate immune system resulting in the existence of a certain-level of intrinsic inflammation that leads to the exacerbating consequences stated above that are seen in depression (Perrin et al., 2019; Horowitz et al., 2020; Yeager et al., 2011). Therefore, it can be speculated that the proposed models may occur simultaneously.

However, considering also the limitations of previous clinical studies, including small sample sizes, there is still a need for additional large mechanistic studies that specifically investigate cortisol's GR-mediated effects on cytokine production in human depression subjects through utilising more comprehensive measures in order to disentangle this relationship.

Acknowledgments and disclosures

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Research funded by the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre (BRC), London, United Kingdom. This work was also supported by the Wellcome Trust strategy award to the Neuroimmunology of Mood Disorders and Alzheimer's Disease (NIMA) Consortium (104025), which is also funded by Janssen, GlaxoSmithKline, Lundbeck and Pfizer.

Dr. Sforzini and Prof. Pariante have received research funding from the from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 853966-2, as part of the EU-PEARL project. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. Prof. Pariante has also received research funding from Johnson & Johnson as part of a program of research on depression and inflammation, and speakers and consultation fees from Lundbeck and Boehringer Ingelheim.

References

Anacker C, Zunszain PA, Carvalho LA, Pariante CM. The glucocorticoid receptor: pivot of depression and of antidepressant treatment? Psychoneuroendocrinology. 2011; 36 (3) 415–425. DOI: 10.1016/j.psyneuen.2010.03.007 [PubMed: 20399565]

Arloth J, Bogdan R, Weber P, Frishman G, Menke A, Wagner KV, Balsevich G, Schmidt MV, Karbalai N, Czamara D, Altmann A, et al. Genetic Differences in the Immediate Transcriptome Response to Stress Predict Risk-Related Brain Function and Psychiatric Disorders. Neuron. 2015; 86 (5) 1189–1202. DOI: 10.1016/j.neuron.2015.05.034 [PubMed: 26050039]

Bellavance MA, Rivest S. The HPA - Immune Axis and the Immunomodulatory Actions of Glucocorticoids in the Brain. Frontiers in immunology. 2014; 5: 136. doi: 10.3389/fimmu.2014.00136 [PubMed: 24744759]

*. Cattaneo A, Ferrari C, Turner L, Mariani N, Enache D, Hastings C, Kose M, Lombardo G, McLaughlin AP, Nettis MA, Nikkheslat N, et al. Whole-blood expression of inflammasome- and glucocorticoid-related mRNAs correctly separates treatment-resistant depressed patients from drug-free and responsive patients in the BIODEP study. Translational psychiatry. 2020; 10 (1) 232. doi: 10.1038/s41398-020-00874-7 [PubMed: 32699209] [Presenting evidence against the “glucocorticoid resistance” model as no clear correlations were identified between inflammatory biomarkers and GR expression mRNA in the whole blood of patients with MDD, but six inflammasome- and glucocorticoid-related mRNAs distinguished treatment-resistant from treatment-responsive individuals]

Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, Craig IW, Anacker C, Zunsztain PA, McGuffin P, Pariante CM. Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2013; 38 (3) 377–385. DOI: 10.1038/npp.2012.191 [PubMed: 22990943]

Chamberlain SR, Cavanagh J, de Boer P, Mondelli V, Jones D, Drevets WC, Cowen PJ, Harrison NA, Pointon L, Pariante CM, Bullmore ET. Treatment-resistant depression and peripheral C-reactive protein. The British journal of psychiatry: the journal of mental science. 2019; 214 (1) 11–19. DOI: 10.1192/bjp.2018.66 [PubMed: 29764522]

Cruz-Topete D, Cidlowski JA. One hormone, two actions: anti- and pro-inflammatory effects of glucocorticoids. Neuroimmunomodulation. 2015; 22 (1-2) 20–32. DOI: 10.1159/000362724 [PubMed: 25227506]

Desmet SJ, De Bosscher K. Glucocorticoid receptors: finding the middle ground. The Journal of clinical investigation. 2017; 127 (4) 1136–1145. DOI: 10.1172/JCI88886 [PubMed: 28319043]

*. Du Preez A, Law T, Onorato D, Lim YM, Eiben P, Musaelyan K, Egeland M, Hye A, Zunszain PA, Thuret S, Pariante CM, et al. The type of stress matters: repeated injection and permanent social isolation stress in male mice have a differential effect on anxiety- and depressive-like behaviours, and associated biological alterations. Translational psychiatry. 2020; 10 (1) 325. doi: 10.1038/s41398-020-01000-3 [PubMed: 32958745] [Some novel insight into the neuroendocrine changes that can take place when exposed to different types of stress, but no results indicating both increased corticosterone reactivity and increased systemic inflammation in response to stress were reported which is not in line with the “glucocorticoid resistance” model]

Farrell C, O'Keane V. Epigenetics and the glucocorticoid receptor: A review of the implications in depression. Psychiatry research. 2016; 242: 349–356. DOI: 10.1016/j.psychres.2016.06.022 [PubMed: 27344028]

Felger JC, Haroon E, Patel TA, Goldsmith DR, Wommack EC, Woolwine BJ, Le NA, Feinberg R, Tansey MG, Miller AH. What does plasma CRP tell us about peripheral and central inflammation in depression? Molecular psychiatry. 2020; 25 (6) 1301–1311. DOI: 10.1038/s41380-018-0096-3 [PubMed: 29895893]

Fried EI, von Stockert S, Haslbeck J, Lamers F, Schoevers RA, Penninx B. Using network analysis to examine links between individual depressive symptoms, inflammatory markers, and covariates. Psychological medicine. 2020; 50 (16) 2682–2690. DOI: 10.1017/S0033291719002770 [PubMed: 31615595]

**. Horowitz MA, Cattaneo A, Cattane N, Lopizzo N, Tojo L, Bakunina N, Musaelyan K, Borsini A, Zunszain PA, Pariante CM. Glucocorticoids prime the inflammatory response of human hippocampal cells through up-regulation of inflammatory pathways. Brain, behavior, and immunity. 2020; 87: 777–794. DOI: 10.1016/j.bbi.2020.03.012 [PubMed: 32194233] [Further evidence of cortisol’s pro-inflammatory effect that was demonstrated to rely on time,

Europe PMC Funders Author Manuscripts

concentration and the GR in human hippocampal progenitor cell model with significant relevance to depression]

Jung SH, Wang Y, Kim T, Tarr A, Reader B, Powell N, Sheridan JF. Molecular mechanisms of repeated social defeat-induced glucocorticoid resistance: Role of microRNA. Brain, behavior, and immunity. 2015; 44: 195–206. DOI: 10.1016/j.bbi.2014.09.015 [PubMed: 25317829]

Kappelmann N, Czamara D, Rost N, Moser S, Schmoll V, Trastulla L, Stochl J, Lucae S, CHARGE inflammation working group. Binder EB, Khandaker GM, Arloth J. Polygenic risk for immuno-metabolic markers and specific depressive symptoms: A multi-sample network analysis study. Brain, behavior, and immunity. 2021; 95: 256–268. DOI: 10.1016/j.bbi.2021.03.024 [PubMed: 33794315]

Lamberts SW. The glucocorticoid insensitivity syndrome. Hormone research. 1996; 45 (Suppl 1) 2–4. DOI: 10.1159/000184815

Liberman AC, Budziñski ML, Sokn C, Gobbini RP, Steininger A, Arzt E. Regulatory and Mechanistic Actions of Glucocorticoids on T and Inflammatory Cells. Frontiers in endocrinology. 2018; 9: 235. doi: 10.3389/fendo.2018.00235 [PubMed: 29867767]

Lin E, Tsai SJ. Epigenetics and Depression: An Update. Psychiatry investigation. 2019; 16 (9) 654–661. DOI: 10.30773/pi.2019.07.17.2 [PubMed: 31455063]

Lynall ME, Turner L, Bhatti J, Cavanagh J, de Boer P, Mondelli V, Jones D, Drevets WC, Cowen P, Harrison NA, Pariante CM, et al. Neuroimmunology of Mood Disorders and Alzheimer's Disease (NIMA) Consortium. Peripheral Blood Cell-Stratified Subgroups of Inflamed Depression. Biological psychiatry. 2020; 88 (2) 185–196. DOI: 10.1016/j.biopsych.2019.11.017 [PubMed: 32000983]

Mariani N, Cattane N, Pariante C, Cattaneo A. Gene expression studies in Depression development and treatment: an overview of the underlying molecular mechanisms and biological processes to identify biomarkers. Translational psychiatry. 2021; 11 (1) 354. doi: 10.1038/s41398-021-01469-6 [PubMed: 34103475]

Matosin N, Halldorsdottir T, Binder EB. Understanding the Molecular Mechanisms Underpinning Gene by Environment Interactions in Psychiatric Disorders: The FKBP5 Model. Biological psychiatry. 2018; 83 (10) 821–830. DOI: 10.1016/j.biopsych.2018.01.021 [PubMed: 29573791]

Ménard C, Pfau ML, Hodes GE, Russo SJ. Immune and Neuroendocrine Mechanisms of Stress Vulnerability and Resilience. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2017; 42 (1) 62–80. DOI: 10.1038/npp.2016.90 [PubMed: 27291462]

Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature reviews. Immunology. 2016; 16 (1) 22–34. DOI: 10.1038/nri.2015.5

Mourtzi N, Sertedaki A, Charmandari E. Glucocorticoid Signaling and Epigenetic Alterations in Stress-Related Disorders. International journal of molecular sciences. 2021; 22 (11) 5964. doi: 10.3390/ijms22115964 [PubMed: 34073101]

Munhoz CD, Lepsch LB, Kawamoto EM, Malta MB, Lima L, Avellar MC, Sapolsky RM, Scavone C. Chronic unpredictable stress exacerbates lipopolysaccharide-induced activation of nuclear factor-kappaB in the frontal cortex and hippocampus via glucocorticoid secretion. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2006; 26 (14) 3813–3820. DOI: 10.1523/JNEUROSCI.4398-05.2006 [PubMed: 16597735]

Munhoz CD, Sorrells SF, Caso JR, Scavone C, Sapolsky RM. Glucocorticoids exacerbate lipopolysaccharide-induced signaling in the frontal cortex and hippocampus in a dose-dependent manner. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2010; 30 (41) 13690–13698. DOI: 10.1523/JNEUROSCI.0303-09.2010 [PubMed: 20943909]

Nettis MA, Lombardo G, Hastings C, Zajkowska Z, Mariani N, Nikkheslat N, Worrell C, Enache D, McLaughlin A, Kose M, Sforzini L, et al. Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: results from a double-blind randomised clinical trial. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2021; 46 (5) 939–948. DOI: 10.1038/s41386-020-00948-6 [PubMed: 33504955]

Nettis MA, Veronese M, Nikkheslat N, Mariani N, Lombardo G, Sforzini L, Enache D, Harrison NA, Turkheimer FE, Mondelli V, Pariante CM. PET imaging shows no changes in TSPO brain density after IFN-α immune challenge in healthy human volunteers. Translational psychiatry. 2020; 10 (1) 89. doi: 10.1038/s41398-020-0768-z [PubMed: 32152285]

Niraula A, Wang Y, Godbout JP, Sheridan JF. Corticosterone Production during Repeated Social Defeat Causes Monocyte Mobilization from the Bone Marrow, Glucocorticoid Resistance, and Neurovascular Adhesion Molecule Expression. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2018; 38 (9) 2328–2340. DOI: 10.1523/JNEUROSCI.2568-17.2018 [PubMed: 29382712]

Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychological medicine. 2019; 49 (12) 1958–1970. DOI: 10.1017/S0033291719001454 [PubMed: 31258105]

*. Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM, Pariante CM, Howes OD. Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain, behavior, and immunity. 2020; 87: 901–909. DOI: 10.1016/j.bbi.2020.02.010 [PubMed: 32113908] [Largest meta-analysis to demonstrate reduced or unchanged variability in inflammatory markers in patients with depression compared to health controls, as well as increased mean levels of pro-inflammatory cytokines in depression]

Palma-Gudiel H, Prather AA, Lin J, Oxendine JD, Guintivano J, Xia K, Rubinow DR, Wolkowitz O, Epel ES, Zannas AS. HPA axis regulation and epigenetic programming of immune-related genes in chronically stressed and non-stressed mid-life women. Brain, behavior, and immunity. 2021; 92: 49–56. DOI: 10.1016/j.bbi.2020.11.027 [PubMed: 33221485]

Pariante CM. Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology. 2017; 27 (6) 554–559. DOI: 10.1016/j.euroneuro.2017.04.001 [PubMed: 28479211]

Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends in neurosciences. 2008; 31 (9) 464–468. DOI: 10.1016/j.tins.2008.06.006 [PubMed: 18675469]

Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. Biological psychiatry. 2001; 49 (5) 391–404. DOI: 10.1016/s0006-3223(00)01088-x [PubMed: 11274650]

Pariante CM, Pearce BD, Pisell TL, Sanchez CI, Po C, Su C, Miller AH. The proinflammatory cytokine, interleukin-1alpha, reduces glucocorticoid receptor translocation and function. Endocrinology. 1999; 140 (9) 4359–4366. DOI: 10.1210/endo.140.9.6986 [PubMed: 10465310]

Perrin AJ, Horowitz MA, Roelofs J, Zunszain PA, Pariante CM. Glucocorticoid Resistance: Is It a Requisite for Increased Cytokine Production in Depression? A Systematic Review and Meta-Analysis. Frontiers in psychiatry. 2019; 10: 423. doi: 10.3389/fpsyt.2019.00423 [PubMed: 31316402]

**. Pitharouli MC, Hagenaars SP, Glanville KP, Coleman J, Hotopf M, Lewis CM, Pariante CM. Elevated C-Reactive Protein in Patients With Depression, Independent of Genetic, Health, and Psychosocial Factors: Results From the UK Biobank. The American journal of psychiatry. 2021; 178 (6) 522–529. DOI: 10.1176/appi.ajp.2020.20060947 [PubMed: 33985349] [Largest study to show that increased inflammation is a core biological feature of depression and this association exists independently from psychosocial and clinical confounding factors]

Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends in immunology. 2006; 27 (1) 24–31. DOI: 10.1016/j.it.2005.11.006 [PubMed: 16316783]

Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. The American journal of psychiatry. 2003; 160 (9) 1554–1565. DOI: 10.1176/appi.ajp.160.9.1554 [PubMed: 12944327]

Russell A, Hepgul N, Nikkheslat N, Borsini A, Zajkowska Z, Moll N, Forton D, Agarwal K, Chalder T, Mondelli V, Hotopf M, et al. Persistent fatigue induced by interferon-alpha: a novel, inflammation-based, proxy model of chronic fatigue syndrome. Psychoneuroendocrinology. 2019; 100: 276–285. DOI: 10.1016/j.psyneuen.2018.11.032 [PubMed: 30567628]

Spies LL, Verhoog N, Louw A. Acquired Glucocorticoid Resistance Due to Homologous Glucocorticoid Receptor Downregulation: A Modern Look at an Age-Old Problem. Cells. 2021; 10 (10) 2529. doi: 10.3390/cells10102529 [PubMed: 34685511]

Vreugdenhil E, Verissimo CS, Mariman R, Kamphorst JT, Barbosa JS, Zweers T, Champagne DL, Schouten T, Meijer OC, de Kloet ER, Fitzsimons CP. MicroRNA 18 and 124a down-regulate the glucocorticoid receptor: implications for glucocorticoid responsiveness in the brain. Endocrinology. 2009; 150 (5) 2220–2228. DOI: 10.1210/en.2008-1335 [PubMed: 19131573]

Weber MD, Godbout JP, Sheridan JF. Repeated Social Defeat, Neuroinflammation, and Behavior: Monocytes Carry the Signal. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2017; 42 (1) 46–61. DOI: 10.1038/npp.2016.102 [PubMed: 27319971]

Xavier AM, Anunciato AK, Rosenstock TR, Glezer I. Gene Expression Control by Glucocorticoid Receptors during Innate Immune Responses. Frontiers in endocrinology. 2016; 7: 31. doi: 10.3389/fendo.2016.00031 [PubMed: 27148162]

Yeager MP, Pioli PA, Collins J, Barr F, Metzler S, Sites BD, Guyre PM. Glucocorticoids enhance the in vivo migratory response of human monocytes. Brain, behavior, and immunity. 2016; 54: 86–94. DOI: 10.1016/j.bbi.2016.01.004 [PubMed: 26790757]

Yeager MP, Pioli PA, Guyre PM. Cortisol exerts bi-phasic regulation of inflammation in humans. Dose-response: a publication of International Hormesis Society. 2011; 9 (3) 332–347. DOI: 10.2203/dose-response.10-013.Yeager [PubMed: 22013396]

Zannas AS, Jia M, Hafner K, Baumert J, Wiechmann T, Pape JC, Arloth J, Ködel M, Martinelli S, Roitman M, Röh S, et al. Epigenetic upregulation of FKBP5 by aging and stress contributes to NF-κB-driven inflammation and cardiovascular risk. Proceedings of the National Academy of Sciences of the United States of America. 2019; 116 (23) 11370–11379. DOI: 10.1073/pnas.1816847116 [PubMed: 31113877]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

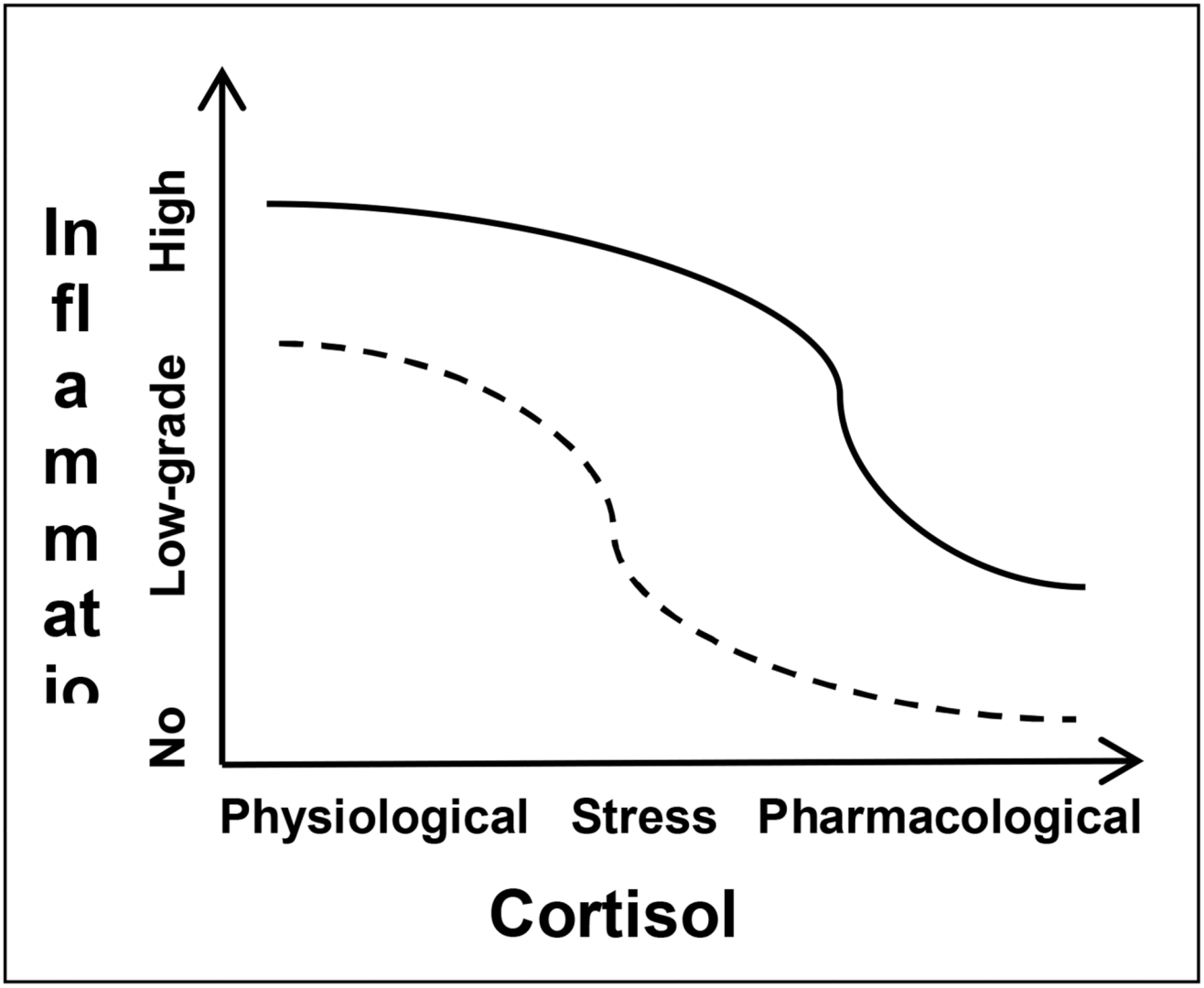

Figure 1. The glucocorticoid resistance model

Europe PMC Funders Author Manuscripts

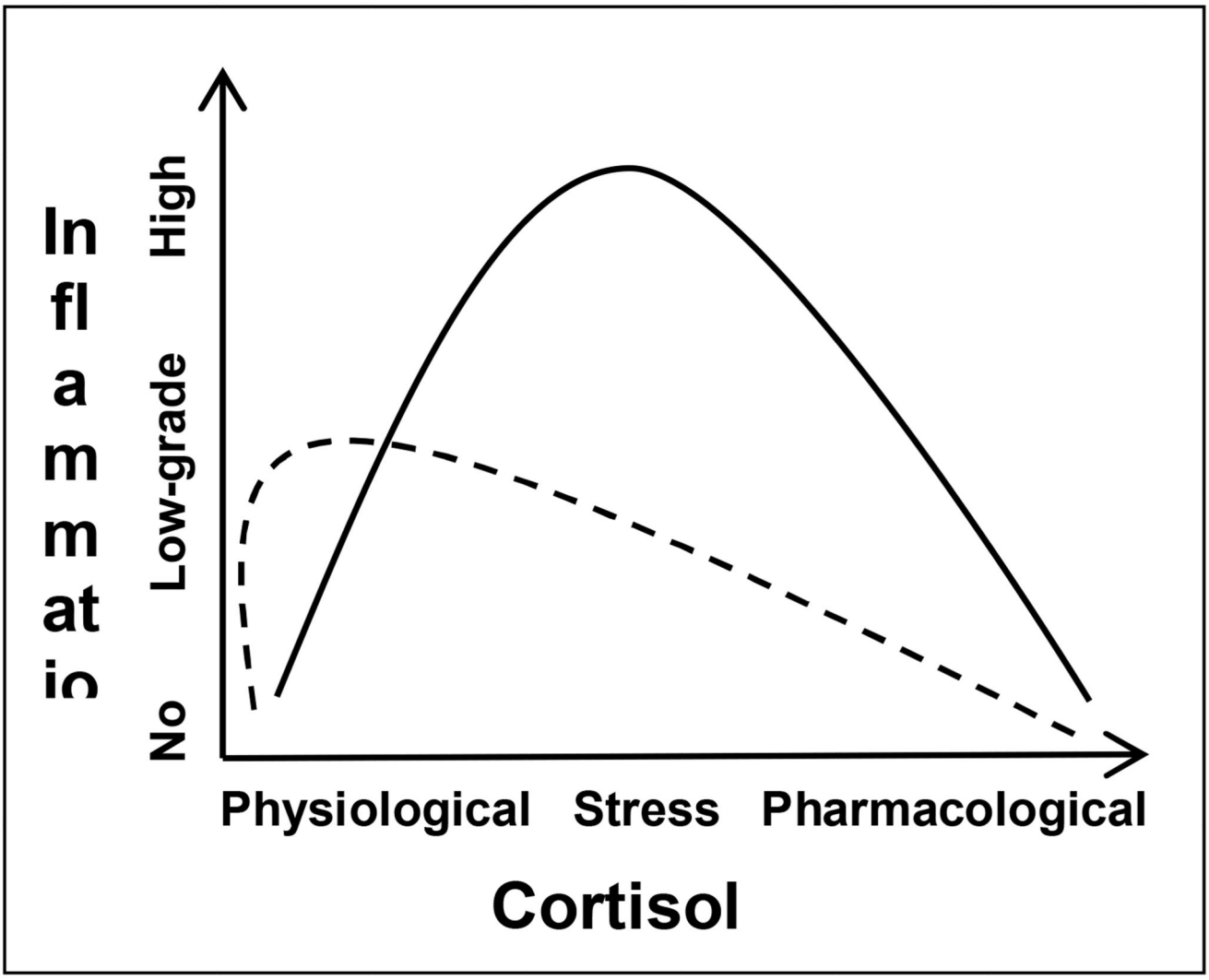

Figure 2. The pro-inflammatory cortisol model