Chapter 14. Physiological Pathways Mediating Between Psychological Stress and Health

Baldwin M. Way[1] and Bert Uchino [2]

[1] Department of Psychology, the Ohio State University

[2] Department of Psychology, University of Utah

Author Note:

Baldwin Way https://orcid.org/0000-0002-9618-0979

Bert Uchino https://orcid.org/0000-0002-3036-6164

Correspondence regarding this chapter should be addressed to:

Baldwin M. Way, Ph.D.

Department of Psychology

The Ohio State University

1735 Neil Avenue

Columbus, OH 43210

way.37@osu.edu

One of the most fascinating questions in Health Psychology is determining how psychosocial experiences influence disease risk and progression. Research on stress has identified several key systems that are critically involved in converting these psychosocial experiences into biological effects that impact disease risk and outcomes. It is these stress-related physiological pathways that are the focus of this chapter. It is intended that this chapter will provide the reader with a basic background on these pathways, current understanding on how they function, as well as several gaps in our current understanding of their effects. After a brief introduction to conceptual models of stress, we will discuss the Sympathetic Nervous System (SNS), the Parasympathetic Nervous System (PNS), the Hypothalamic-Pituitary-Adrenal (HPA) axis, the immune system (particularly linflammation), and the gut microbiota.

By definition, Health Psychology integrates across the psychological and biological domains. This integrative perspective has been core to the field since its inception (Engel, 1977). We adopt this integrative perspective when discussing the physiology as well. Thus, although we discuss the aforementioned physiological pathways as separate systems for conceptual clarity, it should always be in the forefront of the reader's mind that these systems do not function independently of each other. In this vein, we discuss the interactions between these systems in the latter part of this chapter. This focus is consistent with the conceptual work on allostasis on how multiple biological processes are (adaptively) changing in response to environmental needs (Sterling & Eyer, 1988). For example, how do the gut microbiota regulate the HPA axis? Or, how do the HPA axis and immune system interact to influence levels of circulating inflammatory markers?

Stress and the Autonomic Nervous System

The autonomic nervous system (ANS) has historically been viewed as one of the key biological systems linking stress to health given its role in regulating the internal milieu to environmental changes (e.g., fight or flight response). The term ANS was put forth by Langley (Langley, 1921) to characterize the less voluntary nature of such internal responses (at least compared to the somatic nervous system) and separated into the sympathetic nervous system (SNS) and parasympathetic nervous systems (PNS). The SNS is typically seen as the "culprit" underlying stress-related disease processes given its catabolic (energy-expending) influences on end-organ response (e.g., increasing heart rate) that are largely mediated by the postganglionic release of norepinephrine (NE) or epinephrine from the adrenal medulla (Figure 1). The PNS generally has anabolic (energy-conserving) influences on end-organ responses and is mediated by the postganglionic release of acetylcholine (Ach). More recent biomedical and psychological perspectives are increasingly focusing on the PNS as a protective biological response mitigating stress-induced physiological pathways (Brosschot et al., 2017; Tracey, 2002).

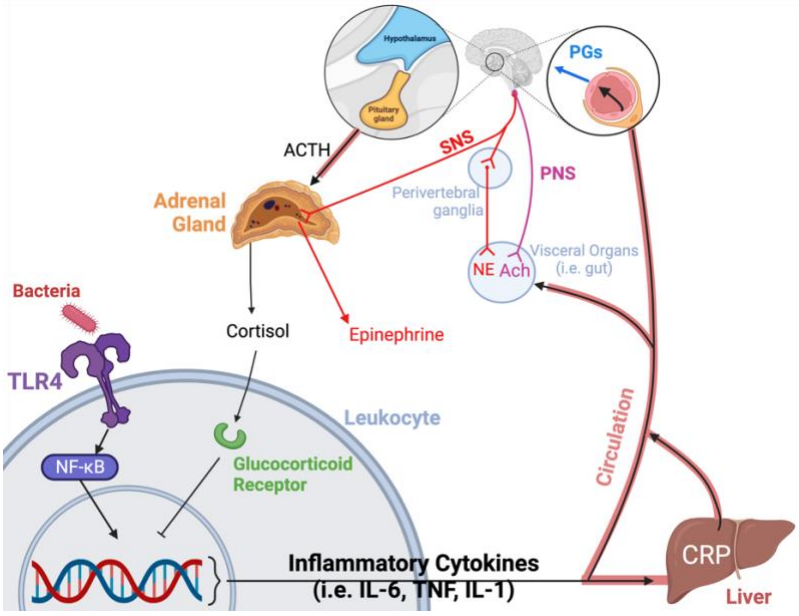

Figure 1. Schematic of the sympathetic nervous system (SNS), parasympathetic nervous system (PNS), hypothalamic pituitary adrenal axis (HPA) axis, and inflammatory pathways. NE =

norepinephrine; Ach = Acetylcholine; CRP = C-Rective Protein; PGs = prostaglandins; ACTH = adrenocotropic hormone; TLR4 = Toll-like Receptor 4.

Much of the work linking stress-induced ANS changes to disease focuses on the reactivity hypothesis (Krantz & Manuck, 1984). This pathway has primarily focused on changes within the cardiovascular system in response to acute laboratory stress and highlights reactivity as a factor in both the development and clinical progression of cardiovascular disease. An important postulate of this model is that lab-based cardiovascular reactivity can provide an index of how individuals' respond to stress in everyday life. The mechanisms responsible for the potential deleterious influences of high stress reactivity in the development of cardiovascular disease includes both direct (e.g., shear stress promoting repeated endothelial injury) and indirect (e.g., release of circulating catecholamines that can promote endothelial injury) pathways. High reactivity might also influence the clinical progression of diagnosed cardiovascular disease as it can precipitate ischemia in such patients (Krantz et al., 1991). Theoretical models highlighting the role of reactivity in disease include the biopsychosocial model of arousal regulation which highlights the role of different appraisal patterns and its link to distinct patterns of cardiovascular reactivity (i.e., cardiac output to challenge, peripheral resistance to threat) that help or hinder energy mobilization (Blascovich & Tomaka, 1996). Recent mindset interventions that focus on decreasing threat appraisals is consistent with this model and appear to have positive influences on well-being, cardiovascular reactivity, and daily cortisol levels (Yeager et al., 2022).

Consistent with the reactivity hypothesis, the magnitude of stress-induced changes in blood pressure reactivity has been linked to future risk for cardiovascular disease including hypertension in otherwise healthy populations (Chida & Steptoe, 2010). One interesting issue to emerge from this literature is that although it has been assumed that higher reactivity is bad for health, there is

also evidence linking lower (blunted) cardiovascular reactivity to worse health outcomes (Brindle et al., 2017). Although more work will be needed to address this potential paradox, blunted reactivity predicting worse health has primary occurred on heart rate reactivity and appear to predict distinct outcomes such as obesity and addiction (Brindle et al., 2017). For instance, consistent with the reactivity hypothesis, the Dutch Famine Birth Cohort Study found that higher SBP reactivity to stress was related to increased risk for hypertension. However, they also found evidence for the risk associated with blunted reactivity because lower heart rate and cortisol reactivity was related to increased risk for obesity (De Rooij, 2013).

The mechanisms responsible for the association between blunted heart rate reactivity and poorer health outcomes remain to be elucidated but may involve motivational processes linked to adverse childhood environments as predicted by the adaptive calibration model (ACM, Brindle et al., 2017; Ellis & Del Giudice, 2019). The ACM is based on a life history perspective and suggest that individuals exposed to childhood adversity are more likely to be on a "fast life course" in which priority is placed on immediate survival and reproduction (Ellis & Del Giudice, 2019). There is some evidence that reactivity patterns may be related to a developmental process in which children raised in high stress environments first show high reactivity (i.e., vigilant), followed by low reactivity (i.e., unemotional) in adolescence in response to increased social competition (Ellis & Del Giudice, 2019). This model does not deny that these patterns have a cost in terms of longer-term health, but is unique in that it highlights the immediate, adaptive significance of biological reactivity for those who are raised in high stress environments. Additional insight into mechanisms might also be garnered by classic psychophysiological studies suggesting that heart rate changes may be part of a central appetitive motivational system reflecting the importance or incentive value of the situation to individuals (Fowles et al., 1982). The findings for blunted reactivity are

important because it starts to move the field away from the general notion that reactivity is bad for health and instead focuses on distinct measures, outcomes, and contextual issues (e.g., effort, performance) that need greater consideration for strong inference (Cacioppo & Tassinary, 1990). One challenge this perspective raises that will require future work is the identification of specific cut-offs for reactivity that would define blunted reactivity in comparison to hyperreactivity.

Consistent with the concept of allostasis (McEwen, 1998), cardiovascular recovery is also an important measure which assesses the ability of the system to return to baseline following stress (Panaite et al., 2015). Although less data exists, delayed cardiovascular recovery has also been shown in meta-analytic reviews to predict future cardiovascular risk in healthy individuals (Chida & Steptoe, 2010; Panaite et al., 2015). A conceptual focus on stress recovery is important because a number of models highlight how a stressor can persist after events have occurred (e.g., rumination; (Brosschot et al., 2017) or how coping factors can influences self-regulatory processes that help individuals recover from stress despite high reactivity (Zee et al., 2020).

Although laboratory protocols have proven valuable in the study of stress and health, studies linking life stress to daily life ambulatory monitoring of cardiovascular function has provided stronger ecological validity. The assessment of both day and night ABP is important because they predict cardiovascular mortality above and beyond conventional blood pressure assessed in the clinic (Parati et al., 2014). One meta-analysis examined the link between job strain and ABP during the day and night in 29 studies (Landsbergis et al., 2013). Cross-sectional analyses showed that exposure to job strain was related to higher ambulatory SBP and DBP, with little evidence for bias in the literature (Landsbergis et al., 2013). There were too few longitudinal studies on the topic to conduct a meta-analysis and existing work was conflicting so more work is needed. However, longitudinal studies in other areas of stress have shown that in the weeks

following bereavement, there is an increase in ABP and a decrease in heart rate variability (HRV), an index of PNS activity, that might explain links to mortality (Buckley et al., 2011, 2012).

Finally, the PNS is increasingly examined as a protective factor in stress-related processes. Acute stress reliably results in vagal withdrawal as indexed by HF-HRV; such lower PNS activity predicts greater cardiovascular and all-cause mortality (Fang et al., 2020). Such associations may be related to conceptual links between the PNS and relevant psychosocial processes although several models which focus on self-regulation and/or social functioning can interpret such links (Smith et al., 2020). For instance, the generalized unsafety model argues that the stress response is our default state which is normally under inhibitory control from the prefrontal cortex when individuals feel safe and results in greater PNS activity (Brosschot et al., 2017). Feelings of unsafety, rather than stressors, release this inhibition and trigger the harmful physiological effects of stress.

Stress and The HPA Axis

Even before delving into the health psychology literature, readers were probably familiar with the principal output of the HPA axis, the glucocorticoid hormone cortisol. Cortisol is the end product of a signaling cascade whereby cells in a nucleus of the hypothalamus are activated in response to psychological stress release Corticotropin Releasing Hormone (CRH) into it's own private set of blood vessels that carry the CRH to the anterior pituitary (Figure 1). Upon receiving CRH, cells in the anterior pituitary trigger the release of adrenocorticotropic hormone (ACTH) into the blood. In the last step, ACTH binds to receptors in the adrenal cortex, which triggers the synthesis of cortisol. Because of cortisol's chemical structure (lipophilic), it can diffuse into the blood and travel to effector sites throughout the brain and body. Consistent with the goal of providing the organism energy to cope with stress or take advantage of a challenge,

cortisol liberates glucose and breaks down proteins and fats to provide fuel for action (Silverman & Sternberg, 2012). The HPA axis signaling cascade is regulated by feedback at the level of the hippocampus, hypothalamus, and anterior pituitary where cortisol can bind to glucocorticoid receptors and reduce or terminate activity within the HPA axis (Russell & Lightman, 2019).

One factor that has facilitated widespread research into the HPA axis is that cortisol can be measured relatively non-invasively using either collection of saliva or hair. With respect to salivary cortisol measurements, there are two main approaches that have been used to understand the HPA axis that will be discussed here: one captures variation in the production of cortisol over the course of the day and the other measures cortisol in response to acute stressors in the laboratory (the cortisol awakening response is also a significant focus of health psychology research; for a review see (Stalder et al., 2016)).

With respect to diurnal cortisol, cortisol levels have a reliable rhythm that peaks in the morning and then tapers off to its lowest levels in the evening (Russell & Lightman, 2019). In order to assess the trajectory of the cortisol response, the participant provides a salivary sample at multiple time points (typically 5-7x per day) across several days. There is a robust body of evidence that a flatter slope -- in other words, cortisol levels staying elevated in the afternoon and evening – is associated with poorer mental and physical health outcomes, including cancer, depression, and obesity (Adam et al., 2017). Several of these studies were prospective, suggesting that it is flatter diurnal cortisol slopes driving the outcomes rather than the other way around. Of note, inflammatory outcomes showed the largest effect sizes in this meta-analysis, underscoring the important interrelationship between these two stress responsive systems that will be discussed later.

In the laboratory, seminal work showed that cortisol reactivity to acute stress is driven most potently by an evaluative, uncontrollable context (Dickerson & Kemeny, 2004). The Trier Social Stress Test has become the most used paradigm to create an uncontrollable, socially-evaluative context: the participant is given minimal time to prepare a speech that is given in front of a small, non-responsive audience. This is followed by performing mental arithmetic while the experimenter pressures the participant to do better and go faster. There is some evidence that males may show more robust cortisol reactivity to the Trier Social Stress Test (J. J. Liu et al., 2017), some of which may be attributable to methodological differences or influences of sex hormones (Gervasio et al., 2021). There is also evidence of cross-cultural differences, with cortisol reactivity being higher in cultures valuing harmony and lower in those valuing mastery (R. Miller & Kirschbaum, 2019). Cultural differences in subjective experience to laboratory stressors are less clear. Interestingly, there is not a close correspondence between psychological distress to the TSST and cortisol reactivity (Campbell & Ehlert, 2012), though perhaps this is an artifact of most studies measuring subjective responses at the end of the task rather than during the stressor (Hellhammer & Schubert, 2012). Nonetheless, it is an important reminder against simple reductionist explanations for biological effects seen in health psychology -- the biological and psychological domains may be capturing different components of the stress reactivity process and shouldn't be viewed as interchangable.

A key question arising from cortisol reactivity studies is the degree to which they can be used to predict future health outcomes. As discussed previously in the autonomic nervous system section, one hypothesis concerning the value of stress reactivity studies is that determining reactivity to stressors in the laboratory will predict reactivity to stressors encountered in daily life. Assuming all individuals regularly encounter stressors, an accumulation of greater reactivity

to these stressors will jeopardize health. Consistent with this hypothesis, greater cortisol reactivity to challenging mental tasks predicted the onset of hypertension and greater coronary artery calcification 3 years later (Hamer et al., 2012; Hamer & Steptoe, 2012). In contrast, just as with cardiovascular reactivity blunted cortisol reactivity is also associated with negative health outcomes (Turner et al., 2020). The variance explained by for either reactivity or blunting predictors are rather low (<5%). There are different ways to interpret these results. On the one hand, it is impressive that reactivity to a single 5-10 minute behavioral test with all its associated variability can predict an important health outcome several years later. On the other hand, one could argue that this suggests weaknesses with the stress reactivity model and other models are needed (Brosschot et al., 2017).

One way to clarify the meaning of these effects is to compare them with the diurnal cortisol literature for which there is more evidence. Unfortunately, this is not well-studied, but from the evidence available there does not appear to be a robust relationship between diurnal cortisol slopes and cortisol reactivity in adults (Kidd et al., 2014) or children/adolescents (Malanchini et al., 2021). This suggests that regulation of acute stress reactivity and regulation of diurnal cortisol are under differential control.

Another potential explanation for the blunted cortisol reactivity is a third variable – that another factor is driving the blunted reactivity and the health outcomes. One such candidate is early life adversity, which is associated with blunted cortisol reactivity, but not flatter diurnal cortisol slopes (Schär et al., 2022). One reason early life adversity may lead to blunted cortisol reactivity is that children have less emotion-regulation capabilities and are thus more likely to be traumatized by events that later in life might be less severe. Accordingly, in a meta-analysis delineating between traumatic stressors and other stressors, the former were associated with

blunted cortisol reactivity, while the latter were associated with heightened cortisol reactivity (Hosseini-Kamkar et al., 2021). In contrast to such situational factors driving differential response, another focus has been on person-factors. For example, people who tend to develop depression after chronic stress have impaired glucocorticoid feedback of the HPA axis and thus higher levels of cortisol, while people who develop PTSD after chronic stress tend to have hyper-responsive feedback of the HPA axis and thus lower cortisol (G. E. Miller et al., 2007). Finally, there may be a temporal aspect to the differential reactivity with initial hyper-reactivity leading to eventual hyporeactivity, as was originally proposed by Selye (Selye, 1946) and is also a component of more contemporary models (e.g. ACM; (Ellis & Del Giudice, 2019) that focus on potential adaptive effects of this blunting such as allowing for greater immune response particularly in the face of conflict associated with subordinate status (Avitsur et al., 2001).

Stress and Inflammation

The immune system evolved to protect humans from pathogens that cause infectious disease. To accomplish this goal, the immune system employs a variety of cells and signaling molecules that are activated upon pathogen detection. Of relevance for health psychologists, psychological stress can activate many of these same cells and signaling pathways. In particular, we focus here on a specific action of the immune system, inflammation. When acute and time limited, inflammation is designed to protect us from pathogens and to also help heal wounds. However, when chronic it can lead to adverse outcomes like cardiovascular disease (Emerging Risk Factors Collaboration et al., 2010) and depression (Mac Giollabhui et al., 2021). We first discuss how pathogens trigger inflammation and introduce the names of the main players in the inflammatory process. Then, we discuss how psychological stress triggers inflammation.

Inflammation is elicited when pathogens (i.e. viruses, bacteria, parasites and fungi) are detected by immune cells. These pathogen detectors are receptors on the surface (or sometimes inside) immune cells. Thus, just like neurons have receptors for detecting neurotransmitters, immune cells (as well as some other cells) have dedicated receptors for detecting bacteria and viruses. These receptors are called pattern recognition receptors (PRR) and one of the most commonly studied receptors is a member of the toll-like receptor family, Toll-like Receptor 4 (TLR4), which resides on the outer surface of immune cells.

Pattern recognition receptors like TLR4 recognize molecular patterns that are specific to pathogens (pathogen-associated molecular patterns; PAMPs). For example, gram negative bacteria such as *E. Coli* have a molecular marker in their cell wall called Lipopolysaccharide (LPS) to which TLR4 binds (Fitzgerald & Kagan, 2020). LPS functions much like a molecular "nametag" or "barcode" (Bullmore, 2018) that labels these cells as bacteria. TLR4 is not only a bacterial detector; it can also detect protein markers on viruses such as Ebola (Lester & Li, 2014). Thus, in some cases, the same pattern recognition receptor can respond to both bacterial and viral infections.

Once the TLR4 receptor and other receptors in this family bind to one of these molecular barcodes, it triggers an intracellular signaling cascade. In other words, there are a series of proteins within the cell that interact with each other to determine the magnitude and nature of the response upon activation of the receptor. A critical protein at the end of this signaling cascade is called NF-KB. Once activated, this protein travels to the nucleus of the cell where the DNA resides. It then can bind to a variety of genes in order to influence their activity levels. Of most relevance for health psychology are a class of proteins involved in signaling between cells called cytokines and chemokines. NF-KB increases the expression of many of these proteins including

the cytokines TNF-α, IL-1β, and IL-6 (T. Liu et al., 2017). NF-KB also has a prominent role in inducing expression of another group of cytokines that is particularly involved in responses to viral pathogens, Interferons (Lester & Li, 2014). These cytokines are then released by immune cells into the nearby tissue or the blood to act on additional immune cells, neurons, or other cells. Thus, cytokines serve as chemical communicators between immune cells – just as neurotransmitters communicate between neurons. This same NF-KB pathway in immune cells can not only be triggered by bacterial and viral stimuli, but also by cytokines in other cells, which can serve to amplify the signal upon pathogen detection.

There is one additional pathway that is triggered upon exposure to pathogens that is important for understanding the inflammatory markers studied by health psychologists. Cytokines that are released into the blood from sites of infection travel to the liver where they induce the expression of a group of proteins that are also involved in helping the body isolate and destroy the pathogen. This response is sometimes referred to as the "acute phase response" based on observations in the 1940's of a protein in the blood that rises to very high levels in the early, acute stages of different types of infection and then decreases with the infection (Cray et al., 2009). This protein was named C-Reactive protein (CRP). The synthesis of CRP is triggered primarily by IL-6, but, to a lesser extent, TNF-α, and IL-1β (Sproston & Ashworth, 2018). Because the aforementioned cytokines and CRP can be measured in blood, they are often measured in health psychology studies as biomarkers of inflammation.

The reason to spend time explaining these complicated signaling pathways is that psychological stress can also activate these pathways. The same protein mentioned above that triggers expression of proinflammatory cytokines after exposure to pathogens, NF-KB, is activated by an acute stressor, the Trier Social Stress Test. The response occurs rapidly: NF-KB

binds to the DNA within 10 minutes of stressor onset (Bierhaus et al., 2003; Kuebler et al., 2015; Wolf et al., 2009). As one would expect following NF-KB binding to DNA, the Trier Social Stress test also leads to increases in the circulating levels of pro-inflammatory cytokines: TNF-α, IL-1β, and IL-6. According to a recent meta-analysis (Marsland et al., 2017), TNF-α peaks first, followed by IL-1β and then IL-6.

With respect to the health implications of inflammatory reactivity to acute stress, there has been comparatively less research than for cortisol or cardiovascular reactivity. Only several studies have looked at this question. As an example, greater IL-6 reactivity to two psychological tasks (color-word interference and mirror tracing) predicted greater ambulatory systolic blood pressure 3 years later (Brydon & Steptoe, 2005). The general assumption is that higher inflammatory reactivity is associated with worse future outcomes. We are not aware of work showing a blunted inflammatory response to acute stress being associated with a particular health outcome, unlike what has been found for cortisol and cardiovascular reactivity. Similarly, there has been less investigation of the return of inflammatory markers to baseline and potential health correlates of stress recovery.

With respect to chronic stress, you guessed it, these same inflammatory pathways are involved. Stressors such as caretaking (G. E. Miller et al., 2008) or low early-life socioeconomic status (G. E. Miller et al., 2009) are associated with increased expression of genes regulated by NF-KB. Because the pattern of stress-induced alterations in gene expression in immune cells within the blood is common across many stressors, particularly social stressors (e.g social safety theory Slavich, 2020), one methodological approach that has become increasingly popular in Health Psychology studies is to measure changes in expression of a set of genes that are associated with inflammation that tend to increase with chronic stress and a set of genes that are

associated with antiviral responses (type I interferon) that tend to be downregulated in chronic stress. This is called the Conserved Transcriptional Response to Adversity (CTRA; (Cole, 2019). The advantage of this approach is that gene expression is a very sensitive measure, though expression does not always correlate with the levels of protein produced. Because proteins are the communicators of the inflammatory signals, they have received the most study in the literature. In general, chronic stress is associated with levels of inflammatory markers that are elevated above those of non-stressed individuals, but not elevated to the same magnitude of someone experiencing an infection. This non-resolving, moderate elevation of inflammatory markers is often referred to as chronic, low-grade inflammation. It has been argued that the majority of the top 10 killers in the United States are associated with this type of chronic inflammation (Furman et al., 2019). IL-6 and CRP are the most commonly studied inflammatory markers in Health Psychology research, though many investigators examine multiple cytokines due to modern methods allowing the ability to assay more than one cytokine at a time. Unfortunately, the field is too nascent for strong theoretical justification at the biological or psychological level for the specific marker chosen. As there is commonality in the activation of these cytokines, some investigators have taken to combing these markers into an inflammatory index. However, concerns have been raised about the reliability of such measures (Moriarity et al., 2021).

By necessity of space limitations, we have introduced the reader to just a thin slice of the immune system that is relevant for Health Psychology and refer the interested reader to more in-depth reviews (Berk et al., 2021) to learn about the parts of the immune system not covered here including the factors involved in resolving inflammation as well as what is called the adaptive arm of the immune system (Dantzer, 2021).

Autonomic Nervous System Pathways and Inflammation

Consistent with the goal of discussing cross-system interactions, a foundational finding on the interrelationship between the parasympathetic nervous system and inflammation was Tracey's work (Tracey, 2002) describing the cholinergic anti-inflammatory reflex. Sensory neurons of the vagus nerve are well-situated to detect peripheral inflammation given they have receptors for cytokines which transmit information to a brainstem nucleus that is a central relay for autonomic function (Alen, 2022). Tracey argued that parasympathetic efferents traveling from the brain via the vagus nerve play a critical role in real-time buffering of inflammatory responses that keeps them limited and localized (Tracey, 2002). In support of this, direct stimulation of the vagus nerve decreases TNF-α production when high levels of LPS containing bacteria are in the blood. Conversely, lesion of the vagus nerve has opposing effects (Tracey, 2002). Finally, noninvasive measures that index parasympathetic activity (ie. HF-HRV) are inversely related to measures of inflammation as shown by a recent meta-analysis (Williams et al., 2019). Thus, the PNS is an important regulator keeping inflammation from becoming elevated.

Although the cholinergic anti-inflammatory effect is well-documented, there is debate about the exact pathways by which this occurs and the role of the SNS (McAllen et al., 2022; Murray & Reardon, 2018). On the one hand, there is evidence that β-blockers, which inhibit norepinephrine signaling from the sympathetic nervous system, reduce the release of highly reactive, newly formed proinflammatory cells from the bone marrow (Powell et al., 2013). Similarly, β-blockers inhibit increases in IL-6 in men (Steptoe et al., 2018) after an acute stressor and similarly inhibit upregulation of proinflammatory genes in men and women after a Trier Social Stress Test (MacCormack et al., 2021). This suggests that the sympathetic nervous system triggers inflammation. On the other hand, localized peripheral SNS activity may dampen inflammatory

responses during challenge (McAllen et al., 2022). For instance, inflammatory mediators are enhanced, not reduced, after local β_2 receptor blockade or sympathetic nerve ablation (McAllen et al., 2022). Potential explanations of these contrasting results are that there may be different direction of effects between the brain, where the SNS activation is proinflammatory (e.g., Soszynski et al., 1996) and the periphery where it isn't. There are also likely to be differential effects due to actions on different immune cells, dependencies on the local inflammatory context (Chiarella et al., 2014), and differential effects at the genomic level due to different interactions with transcription factors like NF-KB (Kolmus et al., 2015). Future research will be needed to qualify the more complex pathways that can be leveraged for clinical use.

Influence of the HPA axis on inflammation

One area of active research in cross-system interactions is the relationship between cortisol and inflammation. Much thinking in this area has been driven by the discovery in the 1940's that synthetic glucocorticoids have immunosuppressive effects (which led to the Nobel Prize in 1950). Since that time, administration of glucocorticoids (colloquially referred to as "steroids") has become a therapeutic mainstay for inflammatory and autoimmune conditions. This compelling clinical evidence has driven the canonical view that glucocorticoids inhibit inflammation. The principal mechanism for this effect is via binding of these synthetic glucocorticoids to the glucocorticoid receptor. Once glucocorticoids bind to this receptor a complex is formed that binds to genomic DNA to influence gene transcription. Glucocorticoid response elements are present in about 20% of genes in the genome, including genes coding for proinflammatory cytokines. Thus, there is evidence that glucocorticoids, including cortisol, can inhibit the expression of most proinflammatory cytokines, including TNF-α, IL-6, and IL-1β, as well as IFN-γ (Cain & Cidlowski, 2017).

This inhibitory effect of cortisol and other glucocorticoids on inflammation has created a bit of a mystery for researchers. If cortisol inhibits inflammation, then why does there tend to be a pairing of high inflammation with high cortisol in conditions associated with chronic stress? For example, depression is often considered a disease of hypercortisolemia (Parker et al., 2003) and at the same time there is growing evidence that elevated inflammation may have a causal role in depression (Raison et al., 2006). If cortisol inhibits inflammation, it would be expected that high levels of cortisol would be associated with lower inflammation. One potential answer to this conundrum has been to postulate that with chronic exposure to cortisol or other glucocorticoids there becomes an insensitivity, or resistance, to it's effects (Raison & Miller, 2003). In other words, the cortisol signal is less efficacious. In colloquial terms, continued high levels of circulating cortisol release is a bit like crying wolf too many times and the glucocorticoid receptor starts to "tune out" cortisol's signaling effects.

A key question for HPA-inflammation cross-talk concerns the degree to which glucocorticoid resistance is an explanation for the non-resolving inflammation in individuals exposed to chronic stress. In other words, is the efficiency of glucocorticoid signaling a moderator of the relationship between cortisol and inflammation?

Stress, Glucocorticoid Resistance, and Inflammation

Glucocorticoid resistance has most commonly been studied in the caretaking stress model, where individual's caring for a child with cancer or a spouse with a terminal disease are compared to control individuals. In cross sectional studies, caregivers reliably show greater glucocorticoid resistance across methodologies, including *ex vivo* functional assays[1] (Bauer et

[1] To measure glucocorticoid resistance *ex vivo,* samples of whole blood, specific immune cell types in blood such as peripheral blood mononuclear cells (primarily lymphocytes and monocytes), or other biopsied tissue are aliquoted into separate test tubes with a consistent concentration of a stimulus such as LPS and varying concentrations of a glucocorticoid in order to determine the degree to which the glucocorticoid inhibits the production of inflammatory

al., 2000; G. E. Miller et al., 2002) as well as reduced expression of genes with glucocorticoid response elements (G. E. Miller et al., 2008, 2014). A longitudinal study of caregivers found that distress predicted subsequent glucocorticoid resistance using a *ex vivo* functional assay 6 and 12 months later (Walsh et al., 2018). This provides insight into the direction of the effect due to the prospective design. Thus, there appears to be robust evidence that chronic stressors can elicit glucocorticoid resistance.

However, for glucocorticoid resistance to be an explanation for the co-occurring high levels of cortisol and inflammation, greater glucocorticoid resistance should be associated with higher circulating inflammatory markers or even moderate the relationship between cortisol and these markers. In the previously discussed longitudinal study of caregivers that demonstrated glucocorticoid resistance, circulating IL-6 levels increased in the caregiving group relative to controls, as would be expected. However, this increase over time was not related to the increase in glucocorticoid resistance (Walsh et al., 2018). Although several of the aforementioned studies found elevation in an inflammatory marker (i.e. CRP or IL-6) as well as glucocorticoid resistance in the stressed group (G. E. Miller et al., 2002; Walsh et al., 2018; Wirtz et al., 2003), only one of these studies assessed the relationship between the two. This is important because even though IL-6 levels and glucocorticoid resistance increased over time in the caregivers in Walsh et al., (2018), there was not a direct relationship between them.

A similarly weak relationship has been found in a recent meta-analysis of glucocorticoid resistance studies and inflammatory markers in patients with depression (Perrin et al., 2019). The weakness of this relationship is particularly surprising because hypercortisolemia has long been considered an important concomitant of depression and inflammation is also thought to be a

proteins such as IL-6 by the stimulus. Glucocorticoid resistance is reflected by less inhibition of LPS driven IL-6 production, in this example.

potential driver of depressive symptomatology. Based on this evidence, it would appear that the relationship between glucocorticoid resistance and the elevations in circulating inflammatory markers seen in depression may not be as straightforward or simple as previously thought.

This complexity is reflective of the larger interrelationship between cortisol and inflammation. For example, in addition to their role in inhibiting the rise in cytokines after stimulation by bacterial ligands like LPS, glucocorticoids are also involved in the resolution of inflammation. Glucocorticoid resistance may be impairing the resolution of inflammation as well (Cain & Cidlowski, 2017), which is not assessed in *ex vivo* assays. Beyond effects at the different stages of inflammation, there are also likely to be dose-dependent effects, as low doses of glucocorticoids have been found to promote inflammatory gene expression, while higher doses inhibit it (Sorrells et al., 2009). Similarly, the effects of glucocorticoids can differ whether given before or after the inflammatory challenge (Yeager et al., 2011). Thus, glucocorticoids can have both anti-inflammatory and pro-inflammatory effects and newer models are needed to integrate this data. One step in this direction has been to propose that at low doses glucocorticoids facilitate responses to inflammatory stimuli by upregulating expression of cytokine receptors and then at high doses downregulate the expression of cytokines (Cain & Cidlowski, 2017). This would make for a more sensitive initiation of the inflammatory response, but also more rapid termination of the inflammatory response. Clearly, it appears that there are many exciting new discoveries to be made about the role of the HPA axis in regulating inflammation.

It is important to point out that communication between the HPA axis and the immune system is not a one-way street. Inflammation can impact HPA axis activity, which was first recognized in the mid-1980's (Besedovsky et al., 1986). Administration of LPS or IL-6 to

humans triggers a robust increase in cortisol (Mastorakos et al., 1993). A key mediator of these effects appears to be the prostaglandin system. Although prostaglandins may not be a household name, drugs that inhibit prostaglandin production are in every household: Acetaminophen (i.e. Tylenol), Aspirin, and Ibuprofen (i.e. Advil). Aspirin and Ibuprofen are in a class of drugs called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) that inhibit prostaglandins. Although not generally considered in this class, acetaminophen also inhibits prostaglandins in the brain (Flower & Vane, 1972), which was first recognized by Sir John Vane as part of his work on prostaglandins that led to receiving the Nobel Prize in 1982. The enzymes responsible for prostaglandin production are a part of the aforementioned CTRA pro-inflammatory index and their expression is regulated by NF-KB. Critically, removal of these genes eliminates the effects of inflammatory cytokines on the HPA axis (Furuyashiki & Narumiya, 2011). Inflammatory cytokines (i.e. TNF-alpha, IL-1β, and IL-6, but not CRP) bind to receptors in at the blood brain barrier, which then trigger the synthesis of prostaglandins that relay the signal into the brain. Because cytokines can't cross the blood-brain-barrier, this is one of the ways peripheral inflammation can be communicated to the brain. It is surprising that there has not been more study of this pathway in light of the widespread use of these drugs, their effects on blunting emotional reactivity (Durso et al., 2015), and their clinical efficacy in the treatment of depression (Köhler-Forsberg et al., 2019). Future research will hopefully shed light on how chronic stress alters the influence of inflammatory cytokines on the HPA axis and how this contributes to the inter-relationship between cortisol and inflammation.

The Gut Microbiota, the HPA Axis, and Inflammation

One of the new kids on the block with respect to the physiological pathways that mediate between the mind and disease is the micro-organisms that live in our gut. It is a bit unnerving to

realize that when you look at yourself in the mirror that there are as many bacterial cells in that image as your own cells. Slightly more, actually (Sender et al., 2016) -- even if you did shower and used mouthwash this morning. Although we tend to associate bacteria with bad breath, foul body odor, and disease, this is just a limited portion of the bacteria that reside within and on us. Many of these bacteria are "friends with benefits" (Cryan et al., 2019), also called commensal bacteria, that can have salubrious impacts on physiological stress pathways.

Within your gut is a whole microbial ecosystem. Most studied are the bacteria, but there are other organisms composing the microbiota such as viruses and fungi that have received less research attention. There are hundreds of bacterial species within a typical person's gut microbial community and like in any neighborhood there is competition and cooperation between it's members. Some bacterial species provide nutrients allowing others to flourish and some bacteria release microbials to kill other bacteria (Zeng et al., 2017). Thus, it is thought that greater diversity of bacteria is more salubrious to prevent any one species from taking control of the neighborhood. When there is imbalance in bacterial species, it is called gut dysbiosis. Dysbiosis is important for health psychology because it has been associated with a variety of health outcomes including obesity, diabetes, depression, and certain forms of cancer (i.e. colorectal).

In addition to being associated with multiple health outcomes, the gut microbiome is highly relevant for health psychology because commonly studied health behaviors have robust influences on the gut microbiota. This is most obvious for diet, where the food we eat directly interacts with the microbiome as it is being digested. But, sleep and exercise also impact the microbiota (Madison & Kiecolt-Glaser, 2019).

As with description of the other stress-relevant physiological pathways, a key to understanding the microbiota's influence on health physiology is to understand the relevant

anatomy (Figure 2). This story begins in the gut, where our food and nutrients are absorbed. Although most microbes transiently pass through the gut and are excreted (Mackos et al., 2017), some setup shop in the lumen where there is an entire microbial ecosystem. The microbial ecosystem in the lumen of the gut is separated from the rest of the body by a mucus layer as well as a layer of cells called the epithelium, which acts like a wall to keep the microbiota contained in the gut.

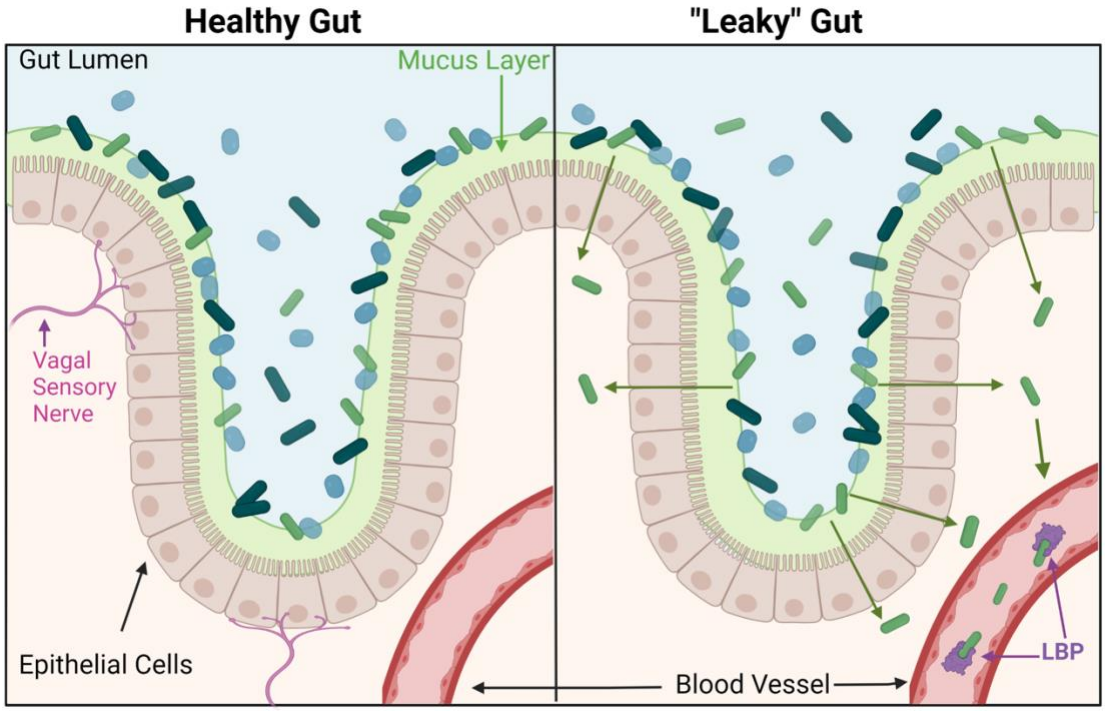

Figure 2. On the left is a depiction of a healthy gut, while on the right is depiction of a "leaky" gut where the junctions between epithelial cells are more porous and bacteria translocate through these gaps into the tissue and blood (denoted by green arrows), where LBP is recruited to cope with the LPS. The vagal afferents are omitted from the right image for clarity of presentation.

The microbiota is becoming increasingly important for Health Psychology because it can influence each of the systems discussed in this chapter. Although the most compelling data

comes from rodent models that have demonstrated proof of principle, there is a growing body of work in humans corroborating these links.

Gut-HPA Axis Communication

With respect to the HPA axis, studies in rodents have shown causal evidence that altering the bacteria in the gut can change hypothalamic neural activation to acute stress, which leads to alterations in circulating glucocorticoid levels (e.g. Ait-Belgnaoui et al., 2012). Of course, a key question is whether this microbiome-HPA axis regulation is occurring in humans as well. One creative way to bridge this gap is to transfer fecal matter from humans to rodents (yes, a poop transplant!). Transfer of fecal microbiome from humans with a clinical diagnosis of depression, a condition associated with HPA axis dysregulation (Parker et al., 2003), into rats, led to heightened circulating glucocorticoid levels relative to fecal microbiota transferred from healthy humans (S. Liu et al., 2020). Human studies have generally used administration of probiotics, which are exogenous live bacteria with the goal of changing the bacterial balance in the gut microbial ecosystem. For example, in a study of 172 Japanese medical students over the 8 weeks leading up to their national examination, a lactic acid probiotic (*Lactobacillus casei*) decreased salivary cortisol responses in the lead up to the exam (Takada et al., 2016). Thus, growing evidence suggests that the gut microbiome can regulate the HPA axis. Interestingly, it appears that these effects might be neurally mediated as lesion of the nerves communicating sensory information (vagal afferents) from the gut to the brain in rodents eliminates the neural and behavioral effects of a probiotic (Bravo et al., 2011). Whether these afferents are triggered by the bacteria themselves, an immune reaction to them, or, most likely, their metabolic byproducts is an area of active research.

Gut Microbiome and Inflammation

In addition to regulating HPA axis signaling, the gut microbiome also impacts inflammatory signaling. Transfer of the microbiome from depressed patients into rats raises circulating levels of TNF-α, IL1, and IL-6 relative to rats receiving fecal transfers from healthy individuals (S. Liu et al., 2020). Furthermore, antibiotic treatment in rodents alters IL-6 levels following acute (Xu et al., 2020) or chronic stress (Bailey et al., 2011). Although most human trials of probiotics have been small, a recent meta-analysis of various probiotic treatments shows beneficial effects on multiple inflammatory markers, including reductions in CRP, IL-6, and TNF-α (Milajerdi et al., 2020).

A key question concerns how gut bacteria can have these effects on inflammation. A likely pathway is via increased gut permeability, colloquially referred to as "leaky gut." The junctions between the cells in the epithelium are dynamically regulated (Mayer et al., 2022). If these cells are like bricks in the wall between the gut and the internal milieu, the junctions between these cells are like the mortar. Various signaling molecules, can strengthen or weaken the "mortar" allowing contents of the gut to escape into the circulation. When cracks in the mortar form, LPS tagged bacteria can make their way into the blood. Once in the blood, TLR4 receptors detect the LPS on these bacteria and trigger an inflammatory cascade, as described previously. One biomarker of this bacterial translocation is Lipopolysaccharide Binding Protein (LBP).

In a study using conflict between romantic partners as a stressor, more hostile interactions predicted higher levels of LBP (Kiecolt-Glaser et al., 2018). These higher levels of LBP were associated with higher levels of circulating CRP, suggesting that translocation of bacteria from the gut to the blood is a potential pathway by which systemic inflammation becomes elevated. As further confirmation of this link, in a longitudinal study of breast cancer survivors, within-

person analyses showed that at time points when relationship satisfaction was higher, LBP levels were lower, which mediated the association between relationship satisfaction and both CRP and IL-6 (Shrout et al., 2022). These increases are likely consequential for health outcomes, as higher LBP concentrations have been found to predict later increases in depressive symptoms (Madison et al., 2020).

An important question for future research is to identify the mechanism responsible for these stress-induced increases in LBP, which presumably reflect greater intestinal permeability. One potential candidate mechanism may be none other than good ol' fashioned cortisol. In a study using a pharmacological approach to measure intestinal permeability, a public speaking stressor was associated with increased intestinal permeability. Critically, the cortisol response to the stressor mediated the effect on intestinal permeability (Vanuytsel et al., 2014). If cortisol can be identified as a contributing culprit to intestinal permeability, it would have important implications for understanding the interrelationship of the HPA axis and inflammation. It would suggest an additional mechanism explaining why high cortisol and high inflammation co-occurs in chronic stress-related conditions. An important future research question will be to determine whether this proposed mechanism or glucocorticoid resistance better explains elevated inflammation.

Conclusions and Future Directions

There are several broad areas of future research salient from this review. Most research in this area has focused on single system biological pathways linking stress to health. As noted in this review, these systems do not exist in isolation and promising work exist modeling interactions across different measures and systems. Of course, such work is more easily done in animal and laboratory research but should not be overlooked in epidemiological studies despite

hurdles associated with measurement issues (e.g., one-time assessments which may contain extraneous sources of error and hence decrease validity and reliability). Indeed, such issues represent challenges that need strong consideration in future epidemiological modeling of psychosocial risk factors, biology, and health.

It will also be important for future work is to include theory-based multilevel analyses that model the complex interface between psychosocial influences and stress-related biology. Most of the prior literature has simply documented links between stress and biology and not made use of theory to guide relevant studies and designs. As noted in several sections, relevant conceptual models exist that integrate psychosocial and biological perspectives (e.g., social safety, generalized unsafety, biopsychosocial model etc.). Such modeling will be important not just for our understanding of antecedent processes/mechanisms but because they highlight efficacious intervention approaches. Included in such approaches is the melding of psychosocial and pharmacological interventions that take into account the complexity of stress-related links to health (Uchino & Way, 2017). Focus on such important future directions is likely to yield both theoretical and applied advances, that in Selye's (1956) words, hold the "secrets of health and happiness" and the "penalties for failure in this great process of adaptation."

References

Adam, E. K., Quinn, M. E., Tavernier, R., McQuillan, M. T., Dahlke, K. A., & Gilbert, K. E. (2017). Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *83*, 25–41. https://doi.org/10.1016/j.psyneuen.2017.05.018

Ait-Belgnaoui, A., Durand, H., Cartier, C., Chaumaz, G., Eutamene, H., Ferrier, L., Houdeau, E., Fioramonti, J., Bueno, L., & Theodorou, V. (2012). Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology*, *37*(11), 1885–1895.

Alen, N. V. (2022). The cholinergic anti-inflammatory pathway in humans: State-of-the-art review and future directions. *Neuroscience and Biobehavioral Reviews*, *136*(December 2021), 104622. https://doi.org/10.1016/j.neubiorev.2022.104622

Avitsur, R., Stark, J. L., & Sheridan, J. F. (2001). Social stress induces glucocorticoid resistance in subordinate animals. *Hormones and Behavior*, *39*(4), 247–257.

Bailey, M. T., Dowd, S. E., Galley, J. D., Hufnagle, A. R., Allen, R. G., & Lyte, M. (2011). Exposure to a social stressor alters the structure of the intestinal microbiota: Implications for stressor-induced immunomodulation. *Brain, Behavior, and Immunity*, *25*(3), 397–407.

Bauer, M. E., Vedhara, K., Perks, P., Wilcock, G. K., Lightman, S. L., & Shanks, N. (2000). Chronic stress in caregivers of dementia patients is associated with reduced lymphocyte sensitivity to glucocorticoids. *Journal of Neuroimmunology*, *103*(1), 84–92.

Berk, M., Leboyer, M., & Sommer, I. E. (2021). *Immuno-Psychiatry*. Springer.

Besedovsky, H., Del Rey, A., Sorkin, E., & Dinarello, C. A. (1986). Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science*, *233*(4764), 652–654.

Bierhaus, A., Wolf, J., Andrassy, M., Rohleder, N., Humpert, P. M., Petrov, D., Ferstl, R., von Eynatten, M., Wendt, T., & Rudofsky, G. (2003). A mechanism converting psychosocial stress into mononuclear cell activation. *Proceedings of the National Academy of Sciences*, *100*(4), 1920–1925.

Blascovich, J., & Tomaka, J. (1996). The Biopsychosocial Model of Arousal Regulation. *Advances in Experimental Social Psychology*, *28*, 1–51. https://doi.org/10.1016/S0065-2601(08)60235-X

Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., Bienenstock, J., & Cryan, J. F. (2011). Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences*, *108*(38), 16050–16055.

Brindle, R. C., Whittaker, A. C., Bibbey, A., Carroll, D., & Ginty, A. T. (2017). Exploring the possible mechanisms of blunted cardiac reactivity to acute psychological stress. *International Journal of Psychophysiology*, *113*, 1–7. https://doi.org/10.1016/j.ijpsycho.2016.12.011

Brosschot, J. F., Verkuil, B., & Thayer, J. F. (2017). Exposed to events that never happen: Generalized unsafety, the default stress response, and prolonged autonomic activity. *Neuroscience and Biobehavioral Reviews*, *74*, 287–296. https://doi.org/10.1016/j.neubiorev.2016.07.019

Brydon, L., & Steptoe, A. (2005). Stress-induced increases in interleukin-6 and fibrinogen predict ambulatory blood pressure at 3-year follow-up. *Journal of Hypertension*, *23*(5), 1001–1007.

Buckley, T., Mihailidou, A. S., Bartrop, R., McKinley, S., Ward, C., Morel-Kopp, M. C., Spinaze, M., & Tofler, G. H. (2011). Haemodynamic Changes During Early Bereavement: Potential Contribution to Increased Cardiovascular Risk. *Heart Lung and Circulation*, *20*(2), 91–98. https://doi.org/10.1016/j.hlc.2010.10.073

Buckley, T., Stannard, A., Bartrop, R., McKinley, S., Ward, C., Mihailidou, A. S., Morel-Kopp, M. C., Spinaze, M., & Tofler, G. (2012). Effect of early bereavement on heart rate and heart rate

variability. *American Journal of Cardiology*, *110*(9), 1378–1383. https://doi.org/10.1016/j.amjcard.2012.06.045

Bullmore, E. (2018). *The inflamed mind: A radical new approach to depression*. Picador.

Cacioppo, J. T., & Tassinary, L. G. (1990). Inferring psychological significance from physiological signals. *The American Psychologist*, *45*(1), 16–28. https://doi.org/10.1037/0003-066X.45.1.16

Cain, D. W., & Cidlowski, J. A. (2017). Immune regulation by glucocorticoids. *Nature Reviews Immunology*, *17*(4), 233–247.

Campbell, J., & Ehlert, U. (2012). Acute psychosocial stress: Does the emotional stress response correspond with physiological responses? *Psychoneuroendocrinology*, *37*(8), 1111–1134. https://doi.org/10.1016/j.psyneuen.2011.12.010

Chiarella, S. E., Soberanes, S., Urich, D., Morales-Nebreda, L., Nigdelioglu, R., Green, D., Young, J. B., Gonzalez, A., Rosario, C., & Misharin, A. V. (2014). β 2-Adrenergic agonists augment air pollution–induced IL-6 release and thrombosis. *The Journal of Clinical Investigation*, *124*(7), 2935–2946.

Chida, Y., & Steptoe, A. (2010). Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: A meta-analysis of prospective evidence. *Hypertension*, *55*(4), 1026–1032. https://doi.org/10.1161/HYPERTENSIONAHA.109.146621

Cole, S. W. (2019). The Conserved Transcriptional Response to Adversity. *Current Opinion in Behavioral Sciences*, *28*, 31–37. https://doi.org/10.1016/j.cobeha.2019.01.008

Cray, C., Zaias, J., & Altman, N. H. (2009). Acute phase response in animals: A review. *Comparative Medicine*, *59*(6), 517–526.

Cryan, J. F., O'Riordan, K. J., Cowan, C. S., Sandhu, K. V., Bastiaanssen, T. F., Boehme, M., Codagnone, M. G., Cussotto, S., Fulling, C., & Golubeva, A. V. (2019). The microbiota-gut-brain axis. *Physiological Reviews*, 1877–2013.

Dantzer, R. (2021). Depression and the Adaptive Immune System. *Textbook of Immunopsychiatry*, 292.

De Rooij, S. R. (2013). Blunted cardiovascular and cortisol reactivity to acute psychological stress: A summary of results from the Dutch Famine Birth Cohort Study. *International Journal of Psychophysiology*, *90*(1), 21–27. https://doi.org/10.1016/j.ijpsycho.2012.09.011

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin*, *130*(3), 355–391. https://doi.org/10.1037/0033-2909.130.3.355

Durso, G. R. O., Luttrell, A., & Way, B. M. (2015). Over-the-Counter Relief From Pains and Pleasures Alike: Acetaminophen Blunts Evaluation Sensitivity to Both Negative and Positive Stimuli. *Psychological Science*, *26*(6), 750–758. https://doi.org/10.1177/0956797615570366

Ellis, B. J., & Del Giudice, M. (2019). Developmental Adaptation to Stress: An Evolutionary Perspective. *Annual Review of Psychology*, *70*(1), annurev-psych-122216-011732. https://doi.org/10.1146/annurev-psych-122216-011732

Emerging Risk Factors Collaboration, Kaptoge, S., Di Angelantonio, E., Lowe, G., Pepys, M. B., Thompson, S. G., Collins, R., & Danesh, J. (2010). C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: An individual participant meta-analysis. *Lancet*, *375*(9709), 132–140. https://doi.org/10.1016/S0140-6736(09)61717-7

Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science*, *196*(4286), 129–136.

Fang, S. C., Wu, Y. L., & Tsai, P. S. (2020). Heart Rate Variability and Risk of All-Cause Death and Cardiovascular Events in Patients With Cardiovascular Disease: A Meta-Analysis of Cohort

Studies. *Biological Research for Nursing*, *22*(1), 45–56. https://doi.org/10.1177/1099800419877442

Fitzgerald, K. A., & Kagan, J. C. (2020). Toll-like receptors and the control of immunity. *Cell*, *180*(6), 1044–1066.

Flower, R. J., & Vane, J. R. (1972). Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). *Nature*, *240*(5381), 410–411.

Fowles, D. C., Fisher, A. E., & Tranel, D. T. (1982). The Heart Beats to Reward: The Effect of Monetary Incentive on Heart Rate. *Psychophysiology*, *19*(5), 506–513. https://doi.org/10.1111/j.1469-8986.1982.tb02577.x

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D. W., Fasano, A., & Miller, G. W. (2019). Chronic inflammation in the etiology of disease across the life span. *Nature Medicine*, *25*(12), 1822–1832.

Furuyashiki, T., & Narumiya, S. (2011). Stress responses: The contribution of prostaglandin E(2) and its receptors. *Nature Reviews. Endocrinology*, *7*(3), 163–175. https://doi.org/10.1038/nrendo.2010.194

Gervasio, J., Zheng, S., Skrotzki, C., & Pachete, A. (2021). The effect of oral contraceptive use on cortisol reactivity to the trier social stress test: A meta-analysis. *Psychoneuroendocrinology*, 105626.

Hamer, M., Endrighi, R., Venuraju, S. M., Lahiri, A., & Steptoe, A. (2012). Cortisol responses to mental stress and the progression of coronary artery calcification in healthy men and women. *PloS One*, *7*(2), e31356. https://doi.org/10.1371/journal.pone.0031356

Hamer, M., & Steptoe, A. (2012). Cortisol responses to mental stress and incident hypertension in healthy men and women. *The Journal of Clinical Endocrinology and Metabolism*, *97*(1), E29-34. https://doi.org/10.1210/jc.2011-2132

Hellhammer, J., & Schubert, M. (2012). The physiological response to Trier Social Stress Test relates to subjective measures of stress during but not before or after the test. *Psychoneuroendocrinology*, *37*(1), 119–124. https://doi.org/10.1016/j.psyneuen.2011.05.012

Hosseini-Kamkar, N., Lowe, C., & Morton, J. B. (2021). The differential calibration of the HPA axis as a function of trauma versus adversity: A systematic review and p-curve meta-analyses. *Neuroscience & Biobehavioral Reviews*, *127*, 54–135.

Kidd, T., Carvalho, L. A., & Steptoe, A. (2014). The relationship between cortisol responses to laboratory stress and cortisol profiles in daily life. *Biological Psychology*, *99*, 34–40.

Kiecolt-Glaser, J. K., Wilson, S. J., Bailey, M. L., Andridge, R., Peng, J., Jaremka, L. M., Fagundes, C. P., Malarkey, W. B., Laskowski, B., & Belury, M. A. (2018). Marital distress, depression, and a leaky gut: Translocation of bacterial endotoxin as a pathway to inflammation. *Psychoneuroendocrinology*, *98*, 52–60. https://doi.org/10.1016/j.psyneuen.2018.08.007

Köhler-Forsberg, O., N. Lydholm, C., Hjorthøj, C., Nordentoft, M., Mors, O., & Benros, M. E. (2019). Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: Meta-analysis of clinical trials. *Acta Psychiatrica Scandinavica*, *139*(5), 404–419.

Kolmus, K., Tavernier, J., & Gerlo, S. (2015). β2-Adrenergic receptors in immunity and inflammation: Stressing NF-κB. *Brain, Behavior, and Immunity*, *45*, 297–310.

Krantz, D. S., Helmers, K. F., Bairey, C. N., Nebel, L. E., Hedges, S. M., & Rozanski, A. (1991). Cardiovascular reactivity and mental stress-induced myocardial ischemia in patients with coronary artery disease. *Psychosomatic Medicine*, *53*(1), 1–12.

Krantz, D. S., & Manuck, S. B. (1984). Acute psychophysiologic reactivity and risk of cardiovascular disease: A review and methodologic critique. *Psychological Bulletin*, *96*(3), 435–464. https://doi.org/10.1037/0033-2909.96.3.435

Kuebler, U., Zuccarella-Hackl, C., Arpagaus, A., Wolf, J. M., Farahmand, F., von Känel, R., Ehlert, U., & Wirtz, P. H. (2015). Stress-induced modulation of NF-κB activation, inflammation-associated gene expression, and cytokine levels in blood of healthy men. *Brain, Behavior, and Immunity*, *46*, 87–95.

Landsbergis, P. A., Dobson, M., Koutsouras, G., & Schnall, P. (2013). Job Strain and Ambulatory Blood Pressure: A Meta-Analysis and Systematic Review. *American Journal of Public Health*, *103*(3), e61. https://doi.org/10.2105/AJPH.2012.301153

Langley, J. (1921). *The autonomic nervous system*. W. Heffer.

Lester, S. N., & Li, K. (2014). Toll-like receptors in antiviral innate immunity. *Journal of Molecular Biology*, *426*(6), 1246–1264.

Liu, J. J., Ein, N., Peck, K., Huang, V., Pruessner, J. C., & Vickers, K. (2017). Sex differences in salivary cortisol reactivity to the Trier Social Stress Test (TSST): A meta-analysis. *Psychoneuroendocrinology*, *82*, 26–37.

Liu, S., Guo, R., Liu, F., Yuan, Q., Yu, Y., & Ren, F. (2020). Gut microbiota regulates depression-like behavior in rats through the neuroendocrine-immune-mitochondrial pathway. *Neuropsychiatric Disease and Treatment*, *16*, 859.

Liu, T., Zhang, L., Joo, D., & Sun, S.-C. (2017). NF-κB signaling in inflammation. *Signal Transduction and Targeted Therapy*, *2*(1), 1–9.

Mac Giollabhui, N., Ng, T. H., Ellman, L. M., & Alloy, L. B. (2021). The longitudinal associations of inflammatory biomarkers and depression revisited: Systematic review, meta-analysis, and meta-regression. *Molecular Psychiatry*, *26*(7), 3302–3314. https://doi.org/10.1038/s41380-020-00867-4

MacCormack, J. K., Gaudier-Diaz, M. M., Armstrong-Carter, E. L., Arevalo, J. M., Meltzer-Brody, S., Sloan, E. K., Cole, S. W., & Muscatell, K. A. (2021). Beta-adrenergic blockade blunts inflammatory and

antiviral/antibody gene expression responses to acute psychosocial stress. *Neuropsychopharmacology*, *46*(4), 756–762.

Madison, A. A., Andridge, R., Padin, A. C., Wilson, S., Bailey, M. T., Alfano, C. M., Povoski, S. P., Lipari, A. M., Agnese, D. M., & Carson, W. E. (2020). Endotoxemia coupled with heightened inflammation predicts future depressive symptoms. *Psychoneuroendocrinology*, *122*, 104864.

Madison, A. A., & Kiecolt-Glaser, J. K. (2019). Stress, depression, diet, and the gut microbiota: Human–bacteria interactions at the core of psychoneuroimmunology and nutrition. *Current Opinion in Behavioral Sciences*, *28*, 105–110.

Malanchini, M., Engelhardt, L. E., Raffington, L. A., Sabhlok, A., Grotzinger, A. D., Briley, D. A., Madole, J. W., Freis, S. M., Patterson, M. W., & Harden, K. P. (2021). Weak and uneven associations of home, neighborhood, and school environments with stress hormone output across multiple timescales. *Molecular Psychiatry*, *26*(9), 4823–4838.

Marsland, A. L., Walsh, C., Lockwood, K., & John-Henderson, N. A. (2017). The effects of acute psychological stress on circulating and stimulated inflammatory markers: A systematic review and meta-analysis. *Brain, Behavior, and Immunity*, *64*, 208–219.

Mastorakos, G., Chrousos, G. P., & Weber, J. S. (1993). Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *The Journal of Clinical Endocrinology & Metabolism*, *77*(6), 1690–1694.

Mayer, E. A., Nance, K., & Chen, S. (2022). The gut–brain axis. *Annual Review of Medicine*, *73*, 439–453.

McAllen, R. M., McKinley, M. J., & Martelli, D. (2022). Reflex regulation of systemic inflammation by the autonomic nervous system. *Autonomic Neuroscience: Basic and Clinical*, *237*(December 2021), 102926. https://doi.org/10.1016/j.autneu.2021.102926

McEwen, B. S. (1998). Protective and damaging effects of stress mediators. *The New England Journal of Medicine*, *338*(3), 171–179. https://doi.org/10.1056/NEJM199801153380307

Milajerdi, A., Mousavi, S. M., Sadeghi, A., Salari-Moghaddam, A., Parohan, M., Larijani, B., & Esmaillzadeh, A. (2020). The effect of probiotics on inflammatory biomarkers: A meta-analysis of randomized clinical trials. *European Journal of Nutrition*, *59*(2), 633–649.

Miller, G. E., Chen, E., Fok, A. K., Walker, H., Lim, A., Nicholls, E. F., Cole, S., & Kobor, M. S. (2009). Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(34), 14716–14721. https://doi.org/10.1073/pnas.0902971106

Miller, G. E., Chen, E., Sze, J., Marin, T., Arevalo, J. M., Doll, R., Ma, R., & Cole, S. W. (2008). A functional genomic fingerprint of chronic stress in humans: Blunted glucocorticoid and increased NF-kappaB signaling. *Biological Psychiatry*, *64*(4), 266–272. https://doi.org/10.1016/j.biopsych.2008.03.017

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin*, *133*(1), 25.

Miller, G. E., Cohen, S., & Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychology*, *21*(6), 531–541. https://doi.org/10.1037/0278-6133.21.6.531

Miller, G. E., Murphy, M. L. M., Cashman, R., Ma, R., Ma, J., Arevalo, J. M. G., Kobor, M. S., & Cole, S. W. (2014). Greater inflammatory activity and blunted glucocorticoid signaling in monocytes of chronically stressed caregivers. *Brain, Behavior, and Immunity*, *41*, 191–199. https://doi.org/10.1016/j.bbi.2014.05.016

Miller, R., & Kirschbaum, C. (2019). Cultures under stress: A cross-national meta-analysis of cortisol responses to the Trier Social Stress Test and their association with anxiety-related value orientations and internalizing mental disorders. *Psychoneuroendocrinology*, *105*, 147–154. https://doi.org/10.1016/j.psyneuen.2018.12.236

Moriarity, D. P., Ellman, L. M., Coe, C. L., Olino, T. M., & Alloy, L. B. (2021). A physiometric investigation of inflammatory composites: Comparison of “a priori” aggregates, empirically-identified factors, and individual proteins. *Brain, Behavior, & Immunity-Health*, *18*, 100391.

Murray, K., & Reardon, C. (2018). The cholinergic anti-inflammatory pathway revisited. *Neurogastroenterology and Motility*, *30*(3), 1–7. https://doi.org/10.1111/nmo.13288

Panaite, V., Salomon, K., Jin, A., & Rottenberg, J. (2015). Cardiovascular recovery from psychological and physiological challenge and risk for adverse cardiovascular outcomes and all-cause mortality. *Psychosomatic Medicine*, *77*(3), 215–226. https://doi.org/10.1097/PSY.0000000000000171

Parati, G., Stergiou, G., O’Brien, E., Asmar, R., Beilin, L., Bilo, G., Clement, D., De La Sierra, A., De Leeuw, P., Dolan, E., Fagard, R., Graves, J., Head, G. A., Imai, Y., Kario, K., Lurbe, E., Mallion, J. M., Mancia, G., Mengden, T., … Zhang, Y. (2014). European society of hypertension practice guidelines for ambulatory blood pressure monitoring. *Journal of Hypertension*, *32*(7), 1359–1366. https://doi.org/10.1097/HJH.0000000000000221

Parker, K. J., Schatzberg, A. F., & Lyons, D. M. (2003). Neuroendocrine aspects of hypercortisolism in major depression. *Hormones and Behavior*, *43*(1), 60–66.

Perrin, A. J., Horowitz, M. A., Roelofs, J., Zunszain, P. A., & Pariante, C. M. (2019). Glucocorticoid resistance: Is it a requisite for increased cytokine production in depression? A systematic review and meta-analysis. *Frontiers in Psychiatry*, *10*, 423.

Powell, N. D., Sloan, E. K., Bailey, M. T., Arevalo, J. M. G., Miller, G. E., Chen, E., Kobor, M. S., Reader, B. F., Sheridan, J. F., & Cole, S. W. (2013). Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via β-adrenergic induction of myelopoiesis. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(41), 16574–16579. https://doi.org/10.1073/pnas.1310655110

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology*, *27*(1), 24–31. https://doi.org/10.1016/j.it.2005.11.006

Raison, C. L., & Miller, A. H. (2003). When not enough is too much: The role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *American Journal of Psychiatry*, *160*(9), 1554–1565.

Russell, G., & Lightman, S. (2019). The human stress response. *Nature Reviews Endocrinology*, *15*(9), 525–534.

Schär, S., Mürner-Lavanchy, I., Schmidt, S. J., Koenig, J., & Kaess, M. (2022). Child maltreatment and hypothalamic-pituitary-adrenal axis functioning: A systematic review and meta-analysis. *Frontiers in Neuroendocrinology*, *66*, 100987.

Selye, H. (1946). The general adaptation syndrome and the diseases of adaptation. *The Journal of Clinical Endocrinology*, *6*(2), 117–230.

Selye, H. (1956). *The stress of life*. McGraw-Hill.

Sender, R., Fuchs, S., & Milo, R. (2016). Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. *Cell*, *164*(3), 337–340.

Shrout, M. R., Madison, A. A., Renna, M. E., Alfano, C. M., Povoski, S. P., Lipari, A. M., Agnese, D. M., Carson III, W. E., Malarkey, W. B., & Bailey, M. T. (2022). The gut connection: Intestinal permeability as a pathway from breast cancer survivors' relationship satisfaction to inflammation across treatment. *Brain, Behavior, and Immunity*, *100*, 145–154.

Silverman, M. N., & Sternberg, E. M. (2012). Glucocorticoid regulation of inflammation and its functional correlates: From HPA axis to glucocorticoid receptor dysfunction. *Annals of the New York Academy of Sciences*, *1261*(1), 55–63.

Slavich, G. M. (2020). Social Safety Theory: A Biologically Based Evolutionary Perspective on Life Stress, Health, and Behavior. *Annual Review of Clinical Psychology*, *16*(1), 1–31. https://doi.org/10.1146/annurev-clinpsy-032816-045159

Smith, T. W., Deits-Lebehn, C., Williams, P. G., Baucom, B. R. W., & Uchino, B. N. (2020). Toward a social psychophysiology of vagally mediated heart rate variability: Concepts and methods in self-regulation, emotion, and interpersonal processes. *Social and Personality Psychology Compass*, *14*(3). https://doi.org/10.1111/spc3.12516

Sorrells, S. F., Caso, J. R., Munhoz, C. D., & Sapolsky, R. M. (2009). The stressed CNS: when glucocorticoids aggravate inflammation. *Neuron*, *64*(1), 33–39.

Sproston, N. R., & Ashworth, J. J. (2018). Role of C-Reactive Protein at Sites of Inflammation and Infection. *Frontiers in Immunology*, *9*, 754. https://doi.org/10.3389/fimmu.2018.00754

Stalder, T., Kirschbaum, C., Kudielka, B. M., Adam, E. K., Pruessner, J. C., Wüst, S., Dockray, S., Smyth, N., Evans, P., & Hellhammer, D. H. (2016). Assessment of the cortisol awakening response: Expert consensus guidelines. *Psychoneuroendocrinology*, *63*, 414–432.

Steptoe, A., Ronaldson, A., Kostich, K., Lazzarino, A. I., Urbanova, L., & Carvalho, L. A. (2018). The effect of beta-adrenergic blockade on inflammatory and cardiovascular responses to acute mental stress. *Brain, Behavior, and Immunity*, *70*, 369–375.

Sterling, P., & Eyer, J. (1988). Allostasis: A New Paradigm to Explain Arousal Pathology. In S. Fisher & J. Reason (Eds.), *Handbook of Life Stress, Cognition and Health* (Issues 629–649). John Wiley & Sons, Ltd.

Takada, M., Nishida, K., Kataoka-Kato, A., Gondo, Y., Ishikawa, H., Suda, K., Kawai, M., Hoshi, R., Watanabe, O., & Igarashi, T. (2016). Probiotic Lactobacillus casei strain Shirota relieves stress-associated symptoms by modulating the gut–brain interaction in human and animal models. *Neurogastroenterology & Motility*, *28*(7), 1027–1036.

Tracey, K. J. (2002). The inflammatory reflex. *Nature*, *420*, 853–859.

Turner, A. I., Smyth, N., Hall, S. J., Torres, S. J., Hussein, M., Jayasinghe, S. U., Ball, K., & Clow, A. J. (2020). Psychological stress reactivity and future health and disease outcomes: A systematic review of prospective evidence. *Psychoneuroendocrinology*, *114*, 104599.

Uchino, B. N., & Way, B. M. (2017). Integrative pathways linking close family ties to health: A neurochemical perspective. *American Psychologist*, *72*(6), 590.

Vanuytsel, T., Van Wanrooy, S., Vanheel, H., Vanormelingen, C., Verschueren, S., Houben, E., Rasoel, S. S., Tóth, J., Holvoet, L., & Farré, R. (2014). Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. *Gut*, *63*(8), 1293–1299.

Walsh, C. P., Ewing, L. J., Cleary, J. L., Vaisleib, A. D., Farrell, C. H., Wright, A. G., Gray, K., & Marsland, A. L. (2018). Development of glucocorticoid resistance over one year among mothers of children newly diagnosed with cancer. *Brain, Behavior, and Immunity*, *69*, 364–373.

Williams, D. W. P., Koenig, J., Carnevali, L., Sgoifo, A., Jarczok, M. N., Sternberg, E. M., & Thayer, J. F. (2019). Heart rate variability and inflammation: A meta-analysis of human studies. *Brain, Behavior, and Immunity*, *80*(February), 219–226. https://doi.org/10.1016/j.bbi.2019.03.009

Wirtz, P. H., Von KÄnel, R., Schnorpfeil, P., Ehlert, U., Frey, K., & Fischer, J. E. (2003). Reduced glucocorticoid sensitivity of monocyte interleukin-6 production in male industrial employees who are vitally exhausted. *Psychosomatic Medicine*, *65*(4), 672–678.

Wolf, J. M., Rohleder, N., Bierhaus, A., Nawroth, P. P., & Kirschbaum, C. (2009). Determinants of the NF-κB response to acute psychosocial stress in humans. *Brain, Behavior, and Immunity*, *23*(6), 742–749.

Xu, C., Lee, S. K., Zhang, D., & Frenette, P. S. (2020). The gut microbiome regulates psychological-stress-induced inflammation. *Immunity*, *53*(2), 417-428. e4.

Yeager, M. P., Pioli, P. A., & Guyre, P. M. (2011). Cortisol exerts bi-phasic regulation of inflammation in humans. *Dose-Response*, *9*(3), dose-response. 10-013. Yeager.

Zee, K. S., Bolger, N., & Higgins, E. T. (2020). Regulatory Effectiveness of Social Support. *Journal of Personality and Social Psychology*, *119*(6), 1316–1358. https://doi.org/10.1037/pspi0000235

Zeng, M. Y., Inohara, N., & Nuñez, G. (2017). Mechanisms of inflammation-driven bacterial dysbiosis in the gut. *Mucosal Immunology*, *10*(1), 18–26.