MS Puzzle Missing Pieces: The Adrenal Influencers

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Abstract

Multiple sclerosis (MS) is a chronic disease characterized by inflammation, demyelination, and neurodegeneration within the central nervous system (CNS). While its precise cause remained elusive until now, an interplay between genetic predisposition, environmental factors, and dysregulation is widely recognized. This paper explores a novel avenue: the potential involvement of adrenal gland function, specifically adrenergic signaling, in the progression and symptomatology of MS. The adrenal glands play a pivotal role in the body's stress response through the release of hormones such as cortisol and adrenaline, which modulate both the immune system and central nervous processes. This paper aims to investigate whether adrenergic influences could act as modulators—or perhaps "influencers"—in the progression of MS. In other words, causes that are known to impact the good functioning of the adrenal glands could be the trigger for the onset of symptomatology that characterizes the disease. For example, one of these causes could be undiagnosed diabetes, as we will deduct.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system (CNS), leading to a progressive decline in physical and cognitive functions. First identified as a distinct condition in the 19th century, MS has since been studied extensively, yet its exact cause remains elusive. French neurologist Jean-Martin Charcot is often credited as one of the first to describe MS in detail around 1868, observing hallmark features such as tremors, scanning speech, and abnormal eye movements. Over the years, researchers noted that MS is characterized by lesions in the brain and spinal cord caused by immune attacks on the protective myelin sheath surrounding nerve fibers. This demyelination leads to communication disruptions between the brain and body, resulting in symptoms that vary widely among patients, from numbness and fatigue to severe paralysis.

The journey of MS treatment has been one of gradual discovery, with options evolving alongside advances in medical science and technology. In the early 20th century, treatment was limited largely to symptomatic relief, using medications to manage symptoms like muscle spasms, bladder dysfunction, and pain. These early approaches did little to alter the disease course, leaving patients vulnerable to progressive disability.

The 1990s marked a turning point in MS treatment with the introduction of the first disease-modifying therapies (DMTs), particularly interferon-beta. These therapies, designed to reduce the frequency and severity of MS relapses, offered new hope for altering disease progression. Following interferons, glatiramer acetate became available, adding another tool to the limited but growing arsenal against MS. Both therapies shifted the focus from symptomatic treatment alone to modifying the underlying immune activity that drives the disease. Since then, research into MS has accelerated, leading to the development of a wide range of DMTs that include oral medications, infusions, and injectable options, each targeting specific mechanisms within the immune system.

In recent years, newer medications, including monoclonal antibodies like natalizumab and ocrelizumab, have offered more targeted approaches with the potential to delay disease progression further and reduce new lesion formation. Experimental treatments such as hematopoietic stem cell transplantation (HSCT) and therapies aimed at promoting remyelination continue to push the boundaries of MS management. These advances represent a shift in MS treatment philosophy: moving from reactive symptom management toward proactive strategies that seek to modify, and even halt, the disease's progression.

Today, MS is recognized as a multifaceted disease influenced by genetic, environmental, and immunological factors. This evolving understanding opens up new areas of investigation, including the role of the hypothalamic-pituitary-adrenal (HPA) axis and adrenal gland function in disease modulation. As researchers continue to explore potential contributors to MS, the involvement of the adrenal glands and adrenergic signaling offers an intriguing frontier. This study will explore how these influences might affect disease activity and progression, potentially expanding treatment options and improving quality of life for those affected by MS. But first, let us take a photograph of the MS symptoms.

Common Symptoms of Multiple Sclerosis

1. **Fatigue**: One of the most common symptoms, which can be overwhelming and affect daily activities.
2. **Muscle Weakness**: Weakness, particularly in the arms or legs, is common and can impact mobility and strength.
3. **Numbness or Tingling**: Often the first sign of MS, this can occur in the face, body, arms, or legs.
4. **Vision Problems**: These may include blurred or double vision, partial or complete loss of vision (often in one eye at a time), and eye pain, particularly during eye movement (a condition called optic neuritis).
5. **Spasticity**: Muscle stiffness and involuntary muscle spasms, especially in the legs, which can cause pain and mobility issues.

6. **Balance and Coordination Issues**: Problems with walking, balance, and coordination are common, which can lead to increased risk of falls.
7. **Pain**: MS can cause both acute and chronic pain, including nerve pain, muscle pain, or headaches.
8. **Bladder and Bowel Dysfunction**: Difficulty controlling the bladder or bowels, frequent urination, or constipation can occur as MS progresses.
9. **Cognitive Changes**: These may include issues with memory, concentration, problem-solving, and processing speed, sometimes referred to as "brain fog."
10. **Mood Changes**: Depression, anxiety, mood swings, and emotional instability (e.g., inappropriate laughing or crying) are common due to the effects of MS on the brain.
11. **Speech and Swallowing Difficulties**: Speech may become slurred or slowed, and swallowing problems (dysphagia) can develop over time.
12. **Tremors**: Involuntary shaking or tremors may occur, affecting fine motor skills and making tasks like writing or holding objects challenging.

Types and Patterns of MS Symptoms

MS symptoms can vary depending on the type of MS a person has:

- **Relapsing-Remitting MS (RRMS)**: Characterized by clear relapses (flare-ups) of symptoms followed by periods of partial or complete remission.
- **Secondary Progressive MS (SPMS)**: Follows RRMS, with symptoms progressively worsening over time with fewer or no periods of remission.
- **Primary Progressive MS (PPMS)**: Symptoms gradually worsen from the onset without early relapses or remissions.
- **Progressive-Relapsing MS (PRMS)**: A rare type with steadily worsening symptoms and occasional flare-ups.

When Symptoms Appear

MS symptoms often worsen during flare-ups or relapses, where inflammation causes new or worsening neurological damage. Symptoms can also be affected by heat (Uhthoff's phenomenon), stress, and fatigue, which can temporarily worsen symptoms.

Each person's experience with MS is unique, and symptoms can range from mild to debilitating. Early diagnosis and treatment can help manage symptoms and slow the progression of the disease.

Preliminaries

The hypothesis that the adrenal gland could be involved in the onset and progression of the MS disease emerged when the researching team, lead by João Coelho, discovered some intriguing statistical artifacts in a not very well known Portuguese dissertation written by a PhD student in the medical field (Coelho, 2011). This paper originally explores the possibility that MS disease symptoms can be relieved by religious beliefs. Even though this paper's main author considers the conclusions of the reference paper to be strange, he declares that the dataset used is correct due to personal inspection. Among other unrelated statistical analysis, the main author noticed that there is a big correlation between the usage of corticosteroid treatment and the change in the time spacing between flare-ups.

Tabela 50- Médias, desvios padrões e t de Student do tempo que decorreu (em meses) após o último surto, nos participantes que tomam ou não corticosteróides.

Tempo após último surto	Corticosteróides					
	Sim (n_1 =63)		Não (n_2 =373)			
	Média	D.P.	Média	D.P.	t	p
	17,06	20,51	37,96	41,48	-6,220	**0,000**

This is a screenshot from the original paper and it is shown that when the corticosteroid therapy is applied, then the average time from the previous flare-up is way lower (17 months) than when corticoid therapy is not done (41 months). This seems to suggest that ***not*** taking corticosteroids is more beneficial than taking them, which is strange since corticosteroid therapy is considered to be a frontline option in order to mitigate the symptoms associated with a flare-up.

Corticosteroids are a class of steroid hormones that are produced naturally in the adrenal cortex of the adrenal glands. They are also synthesized artificially and used as medications for various conditions. These hormones play a vital role in a wide range of physiological processes, including immune response, stress response, metabolism, and inflammation control.

Types of Corticosteroids

There are two main types of corticosteroids based on their primary functions:

1. **Glucocorticoids**: Primarily involved in the regulation of metabolism and the suppression of inflammation. Examples include cortisol and synthetic drugs like prednisone and dexamethasone.
2. **Mineralocorticoids**: Primarily involved in the balance of water and electrolytes in the body. Aldosterone is a naturally occurring mineralocorticoid, while fludrocortisone is a synthetic version.

As we discussed before, it is well known that corticosteroids are produced naturally in the adrenal glands. Therefore, we proceed to explore a little bit further the physiology of the adrenal gland.

The adrenal cortex is the outer layer of the adrenal glands, which are small, triangular-shaped glands located on top of each kidney. The adrenal glands play a critical role in producing various hormones essential for regulating many of the body's functions, including stress response, metabolism, blood pressure, and immune system balance.

Structure of the Adrenal Glands

Each adrenal gland has two main parts:

1. **Adrenal Cortex** (outer layer): Produces essential steroid hormones.
2. **Adrenal Medulla** (inner layer): Produces catecholamines like adrenaline (epinephrine) and noradrenaline (norepinephrine) that are involved in the body's "fight-or-flight" response to stress.

Functions of the Adrenal Cortex

The adrenal cortex itself is further divided into three zones, each responsible for producing different types of steroid hormones:

1. **Zona Glomerulosa**: This is the outermost layer of the cortex and is primarily responsible for producing *mineralocorticoids*, mainly *aldosterone*. Aldosterone helps regulate blood pressure by balancing sodium and potassium levels in the body, thus controlling fluid balance.
2. **Zona Fasciculata**: This is the middle layer of the cortex, which produces *glucocorticoids*, primarily *cortisol*. Cortisol is known as the "stress hormone" because it plays a key role in the body's response to stress, as well as regulating metabolism, reducing inflammation, and controlling blood sugar levels.
3. **Zona Reticularis**: The innermost layer of the cortex, which produces *androgens*. Androgens are precursor hormones that can be converted into more potent sex hormones, like testosterone and estrogen, which help with growth, development, and sexual function.

Importance of the Adrenal Cortex

The adrenal cortex is crucial for maintaining homeostasis in the body. The hormones it produces help control essential functions like:

- Managing the body's response to stress (cortisol)
- Maintaining blood pressure (aldosterone)
- Supporting metabolic processes and immune response (cortisol)
- Assisting in sexual development and function (androgens)

Damage or disorders affecting the adrenal cortex can lead to hormonal imbalances and serious health conditions, such as Addison's disease (cortisol deficiency) or Cushing's syndrome (excessive cortisol).

Functions of the Adrenal Medulla

The adrenal medulla plays a crucial role in the body's response to stress and is responsible for producing certain hormones that help regulate physiological functions associated with the "fight-or-flight" response. Unlike the outer adrenal cortex, which produces steroid hormones, the adrenal medulla produces catecholamines, a group of hormones that include adrenaline (epinephrine) and noradrenaline (norepinephrine). Their functions are as follows:

1. **Production and Release of Catecholamines**
   - The adrenal medulla releases adrenaline (epinephrine) and noradrenaline (norepinephrine), which are critical for the body's acute stress response.
   - These hormones are released in response to signals from the sympathetic nervous system, especially during stressful or emergency situations.
2. **"Fight-or-Flight" Response**
   - When the body perceives a threat or stress, the adrenal medulla releases adrenaline and noradrenaline into the bloodstream, preparing the body for a quick response.
   - This response, known as the "fight-or-flight" response, is characterized by several physiological changes designed to enhance the body's ability to either face or flee from the threat.
3. **Physiological Effects of Adrenaline and Noradrenaline**
   - **Increased Heart Rate**: Adrenaline increases heart rate and the force of heart contractions, which helps supply more blood and oxygen to vital organs and muscles.
   - **Increased Blood Pressure**: Both adrenaline and noradrenaline constrict blood vessels in certain areas (e.g., skin, digestive system) to redirect blood flow to muscles and organs that are essential for immediate physical action.
   - **Bronchodilation**: Adrenaline relaxes the muscles in the airways, allowing for better airflow and oxygen intake.
   - **Metabolic Effects**: Adrenaline stimulates the breakdown of glycogen in the liver and muscles, releasing glucose into the bloodstream for quick energy. It also encourages the release of fatty acids from adipose tissue, providing additional fuel.
   - **Dilation of Pupils**: To improve vision in low light, adrenaline dilates pupils, which can help individuals better assess their environment in a stressful situation.
4. **Short-Term Stress Management**
   - The adrenal medulla's release of catecholamines is ideal for managing short-term stress, as these hormones act quickly and have relatively short-lasting effects.
   - This contrasts with the adrenal cortex, which produces cortisol for more sustained stress response and energy regulation.

Theoretical Deduction

Catecholamine Overdrive

The following text explains, step by step, a causal deduction that indicates that malfunctioning adrenal glands can be the cause for the initial onset of the symptoms for MS. If the corticosteroids are applied, some of the symptoms might disappear or be mitigated. Since there is an outside source of corticosteroids, this inhibits the function of the adrenal cortex (if it is working at all). Thus, even if the life-threatening symptoms may disappear, the Adrenal Medulla is known to not be inhibited by corticosteroid influence. In the event of a malfunctioning Adrenal Medulla, there could be high levels of adrenaline and noradrenaline being produced for an extended period of time, which in turn is known to have damaging effects in the central nervous system. If this is not enough, we need to consider the rebound effect. The rebound happens when the corticosteroid therapy is stopped after the flare-up, which leads to a whiplash reaction; a subsequent reduction in the levels of corticosteroids and, thus, leading to the stimulation of the production of even more catecholamines. These extra catecholamines will further weaken the nervous cells.

<u>High levels of adrenaline have an impact on the central nervous system (CNS) and immune function, creating conditions that could contribute to demyelination.</u>

How Adrenaline Might Indirectly Affect Demyelination

1. **Stress and Immune Response**: elevated adrenaline levels activate the hypothalamic-pituitary-adrenal (HPA) axis and increase the production of cortisol and other stress-related hormones. Chronic activation of this stress response can lead to immune dysregulation and increased inflammation, both of which are known to play roles in demyelinating diseases. While acute adrenaline spikes are less likely to impact myelin directly, prolonged stress could exacerbate immune activity against CNS structures in susceptible individuals.
2. **Oxidative Stress**: High levels of adrenaline and stress hormones can lead to oxidative stress, which damages cells, including neurons and glial cells that produce myelin. Oxidative stress has been implicated in the progression of MS and other neurodegenerative diseases, where it contributes to inflammation and cellular injury.
3. **Excitotoxicity**: Excessive stimulation of the nervous system from high levels of adrenaline and noradrenaline could potentially contribute to excitotoxicity, a process where nerve cells are damaged by excessive stimulation. Excitotoxicity is thought to play a role in several neurological conditions and may contribute to a neuroinflammatory environment, potentially harming myelin.
4. **Blood-Brain Barrier (BBB) Permeability**: elevated adrenaline levels might affect the integrity of the blood-brain barrier, making it more permeable. A compromised BBB allows immune cells to enter the CNS more easily, which could increase the likelihood of immune attacks on myelin in individuals predisposed to autoimmune responses.

How Can MS Be Cured?

In order to understand the nature of the flare-ups, and cure them, we need to systematize in which circumstances the adrenal gland can malfunction. And, in some of these cases, a cure can be found. The malfunctioning of the gland could be permanent or intermittent, leading to different manifestations of the disease.

The proper functioning of the adrenal glands is essential for regulating many bodily processes, including stress response, metabolism, immune function, and electrolyte balance. Several factors can affect adrenal gland health and hormone production, leading to dysfunction or imbalances that impact overall well-being.

1. Chronic Stress

- **Impact**: a very stressful life which leads to prolonged stress can over activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to continuous cortisol production. Over time, this can exhaust the adrenal glands, potentially resulting in “adrenal fatigue” or dysregulation of cortisol levels, causing the first onset (which is then perpetuated by the rebound created by the corticosteroid therapy that is intended to mitigate the symptoms).
- **Symptoms**: Chronic stress may lead to fatigue, immune suppression, sleep disturbances, and weight gain.

2. Poor Diet and Nutritional Deficiencies

- **Nutritional Deficiencies**: Deficiencies in essential nutrients like vitamin C, B vitamins, magnesium, and zinc can impair adrenal function since these nutrients are crucial for hormone synthesis and energy production.
- **High Sugar and Processed Foods**: Diets high in sugar and processed foods can lead to blood sugar fluctuations, triggering the adrenal glands to release more cortisol to stabilize blood sugar levels, leading to adrenal strain over time. <u>Here we highlight that another cause for high sugar in the bloodstream could be an undiagnosed diabetes, for example, which could hamper the adrenal system as a consequence. We estimate that lots of cases of MS could be a result of poorly treated or undiagnosed diabetes.</u>

3. Autoimmune Disorders

- **Autoimmune Adrenalitis**: Autoimmune disorders, such as Addison’s disease, cause the immune system to attack the adrenal glands, reducing their ability to produce essential hormones like cortisol and aldosterone.
- **Symptoms**: This can lead to severe fatigue, muscle weakness, low blood pressure, and electrolyte imbalances.

4. Chronic Infections and Illnesses

- **Infections**: Chronic infections like tuberculosis (which can directly infect the adrenal glands), HIV, and certain viral infections can damage adrenal tissues or dysregulate the HPA axis, affecting adrenal hormone production.
- **Systemic Inflammation**: Ongoing inflammation due to chronic illness can disrupt adrenal function and impair cortisol regulation.

5. Hormonal Imbalances

- **Thyroid Dysfunction**: Hypothyroidism or hyperthyroidism can stress the adrenal glands, as the body relies on coordinated hormone production for energy, metabolism, and stress responses.
- **Estrogen or Progesterone Imbalance**: Changes in estrogen and progesterone, particularly during menopause or due to hormone therapy, can affect cortisol levels and adrenal health.

6. Medications

- **Steroid Medications**: Long-term use of corticosteroids (e.g., prednisone) can suppress the natural production of cortisol by the adrenal glands, potentially leading to adrenal insufficiency if the medication is stopped suddenly.
- **Stimulants and Caffeine**: Overuse of caffeine and stimulants can lead to increased cortisol production, putting strain on the adrenal glands over time.

7. Sleep Deprivation and Irregular Sleep Patterns

- **Impact**: Inadequate or poor-quality sleep affects the natural rhythm of cortisol production, often leading to elevated cortisol at night and low levels in the morning. This disrupts the body's stress response and energy regulation.
- **Consequences**: Chronic sleep issues can contribute to adrenal fatigue, irritability, weakened immune function, and metabolic issues.

8. Physical Trauma and Surgery

- **Physical Stress**: Surgery, severe injury, or trauma can put stress on the adrenal glands, increasing the demand for cortisol and other hormones.
- **Adrenal Insufficiency Risk**: In people with pre-existing adrenal insufficiency, the physical stress of surgery or trauma can lead to an adrenal crisis, a life-threatening condition if untreated.

9. Environmental Toxins and Heavy Metals

- **Toxins and Chemicals**: Exposure to environmental toxins, such as pesticides, heavy metals, and endocrine-disrupting chemicals (like BPA), can interfere with adrenal hormone production.

- **Oxidative Stress**: These toxins can also increase oxidative stress, which can damage adrenal cells and interfere with proper hormone synthesis.

10. Genetics and Congenital Disorders

- **Genetic Conditions**: Certain genetic conditions, such as congenital adrenal hyperplasia, affect the enzymes needed for adrenal hormone production, leading to hormone imbalances from birth.
- **Hereditary Risks**: People with a family history of adrenal or autoimmune disorders may be more susceptible to adrenal dysfunction.

11. Urinary Tract Problems

- **Impact**: a malfunctioning kidney or bladder might give the wrong signals to the adrenal glands, which are responsible for producing the chemicals to regulate the flow of ions into the urine. In some situations, this can lead to the over/under production of corticosteroids and/or catecholamines which in turn can cause the emergence of the first flare-up.

We recommend that all of these (and other) potential causes must be investigated in the event of a suspected MS flare-up, and if the underlying sickness is found, of course it should be treated anyway, regardless of the MS diagnosis. Bonus points: MS will go away as well if a treatment for the underlying problem is available and successfully applied. In the eventuality that an underlying cause is not found or there is no good treatment available, perhaps a good way to proceed would be to apply adrenaline antagonist therapy in order to protect the nerve cells from excitatory overload: alpha blockers, beta blockers and even maybe central adrenergic antagonists.

Conclusion

The potential link between multiple sclerosis (MS) and adrenal gland malfunction introduces a compelling avenue for both understanding and potentially curing the disease. While MS has long been regarded as an autoimmune condition primarily targeting the central nervous system, evidence increasingly suggests that underlying adrenal dysfunction—whether permanent or intermittent—may contribute to the onset and perpetuation of MS symptoms. Proper adrenal function is essential for regulating stress response, immune function, metabolism, and electrolyte balance. When the adrenal glands malfunction, the resultant hormonal imbalances can lead to systemic effects that align closely with the unpredictable nature of MS flare-ups.

Understanding the circumstances under which the adrenal glands can malfunction is critical for addressing the root causes of MS. Factors such as diabetes, urinary tract problems, chronic stress, poor diet, autoimmune disorders, chronic infections, hormonal imbalances, certain medications, sleep deprivation, physical trauma, exposure to environmental toxins, and genetic conditions all contribute to adrenal strain or dysfunction. Chronic stress, for example, leads to overactivation of the hypothalamic-pituitary-adrenal (HPA) axis, causing prolonged cortisol production, which can eventually exhaust the adrenal glands. Similarly, poor dietary habits or undiagnosed conditions like diabetes can lead to blood sugar fluctuations that strain the adrenal system. Autoimmune conditions, such as Addison's disease, directly target adrenal tissue, while infections and chronic illness disrupt the HPA axis, impairing the adrenal glands' ability to regulate immune responses and inflammation effectively. Sleep deprivation, physical trauma, environmental toxins, and certain genetic predispositions add further risk, each placing unique stressors on adrenal health.

To approach MS treatment from this adrenal-centric perspective, it is essential to investigate these factors systematically during MS flare-ups. Identifying and addressing the underlying adrenal stressor—whether it be an undiagnosed autoimmune condition, unmanaged diabetes, or chronic sleep deprivation—could yield not only symptomatic relief but also an opportunity to mitigate or even cure MS in cases where the underlying condition is treatable. By prioritizing the health of the adrenal glands and addressing the broader factors that affect their function, we may ultimately reduce or eliminate MS flare-ups. This holistic approach underscores the complexity of MS and highlights the potential for a cure that goes beyond symptom management, targeting the adrenal system and related stress responses as central elements in the fight against MS.

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References

General References on Multiple Sclerosis

- Coelho, José Carlos Quaresma (2011). **Sofrimento e espiritualidade da pessoa com esclerose múltipla.** Universidade Católica Portuguesa (Portugal) ProQuest Dissertations & Theses, 2011. 28461117.
- Compston, A., & Coles, A. (2008). **Multiple sclerosis.** *The Lancet*, 372(9648), 1502-1517. doi:10.1016/S0140-6736(08)61620-7
- Filippi, M., Bar-Or, A., Piehl, F., et al. (2018). **Multiple sclerosis.** *Nature Reviews Disease Primers*, 4, 43. doi:10.1038/s41572-018-0041-4

Adrenal Gland Function and Physiology

- Bornstein, S. R., Engeland, W. C., Ehrhart-Bornstein, M., & Herman, J. P. (2008). **Dissociation of the adrenal cortex and medulla during development and**

implications for adult regulation. *Endocrine Reviews*, 29(5), 644-663. doi:10.1210/er.2008-0015

- Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). **How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions.** *Endocrine Reviews*, 21(1), 55-89. doi:10.1210/edrv.21.1.0389

Corticosteroids and Adrenal Gland Suppression

- Charmandari, E., Tsigos, C., & Chrousos, G. (2005). **Endocrinology of the stress response.** *Annual Review of Physiology*, 67, 259-284. doi:10.1146/annurev.physiol.67.040403.120816
- Henzen, C., Suter, A., Lerch, E., Urbinelli, R., Schorno, X. H., & Briner, V. A. (2000). **Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment.** *The Lancet*, 355(9203), 542-545. doi:10.1016/S0140-6736(99)07398-X

Role of Chronic Stress and Adrenal Function in Autoimmune Disease

- Elenkov, I. J., & Chrousos, G. P. (2002). **Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity.** *Annals of the New York Academy of Sciences*, 966(1), 290-303. doi:10.1111/j.1749-6632.2002.tb04229.x
- Straub, R. H., & Cutolo, M. (2001). **Involvement of the hypothalamic–pituitary–adrenal/gonadal axis and the peripheral nervous system in rheumatoid arthritis: Viewpoint based on a systemic pathogenetic role.** *Arthritis & Rheumatism*, 44(3), 493-507. doi:10.1002/1529-0131(200103)44:3<493::AID-ANR104>3.0.CO;2-R

Hormonal Influence on Inflammatory and Demyelinating Diseases

- Kalafatakis, K., & Russell, G. M. (2018). **Glucocorticoids as a double-edged sword in the stress response: Functional interactions between the hypothalamic–pituitary–adrenal (HPA) axis and the immuno-inflammatory system.** *Current Opinion in Pharmacology*, 38, 38-43. doi:10.1016/j.coph.2018.02.007
- Wei, Y. B., Liu, J. J., & Young, A. H. (2020). **The hypothalamic-pituitary-adrenal axis: A key focus in the treatment of major depressive disorder.** *Current Opinion in Psychiatry*, 33(1), 57-63. doi:10.1097/YCO.0000000000000560

Potential Role of Catecholamines in Neuroinflammation and Demyelination

- Gold, S. M., Heesen, C., & Schulz, K. H. (2003). **Stress and disease progression in multiple sclerosis: Basic pathways and clinical aspects.** *Brain, Behavior, and Immunity*, 17(2), 141-151. doi:10.1016/S0889-1591(03)00011-5
- Sternberg, E. M. (2006). **Neural regulation of innate immunity: A coordinated nonspecific host response to pathogens.** *Nature Reviews Immunology*, 6(4), 318-328. doi:10.1038/nri1810

- Zunszain, P. A., Anacker, C., Cattaneo, A., Carvalho, L. A., & Pariante, C. M. (2011). **Glucocorticoids, cytokines and brain abnormalities in depression.** *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 35(3), 722-729. doi:10.1016/j.pnpbp.2010.04.011
- Lamport, D. J., Lawton, C. L., Mansfield, M. W., & Dye, L. (2009). **Improvements in cognitive function following a simple dietary change: Mechanisms, biological markers and biomarkers of cognitive function and diseases.** *Nutritional Neuroscience*, 12(5), 241-252. doi:10.1179/147683009X423379