



A review on hypothalamo-pituitary- adrenal axis

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Abstract

The effector hormones of the hypothalamic-pituitary-adrenal axis neuroendocrine system are the glucocorticoid hormones cortisol and corticosterone. The level of corticosterone, a systemic intercellular signal, changes dynamically with environmental and psychological stressors and predictably varies with time of day. A wide range of physiological and mental health issues are linked to irregularities in the typical HPA axis activity profiles. Despite several investigations that have uncovered molecular, cellular, and systems-level glucocorticoid actions to date, more glucocorticoid actions, and connections with clinical state, need to be discovered. Hypothalamic-pituitary-adrenal (HPA) axis feedback regulation may be compromised due to reduced mineralocorticoid receptor (MR)-mediated feedback in the brain. Medicinal herbs and their compounds have been shown to have a preventative impact against depression through a variety of ways. Medicinal plants can provide fresh ideas for antidepressant medication research.

Keywords: hormones, neuroendocrine system, pituitary gland.

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Introduction

The Neuroendocrine Hypothalamic-Pituitary-Adrenal (HPA) axis controls the generation and secretion of glucocorticoids. Changes in HPA axis activity profiles are related to the frequency of pathological biomedical diseases. Changes in HPA axis activity profiles are related to the prevalence of pathological biomedical diseases. Some mental health illnesses, such as depression, Posttraumatic stress disorder and schizophrenia, as well as other biological conditions like Type II diabetes, hypertension, chronic fatigue syndrome, fibromyalgia, and chronic facial pain, are linked to dysregulation of HPA axis activities. A chronic mental or physical stressor might have negative health repercussions due to altered glucocorticoid hormone levels. Changes in basal glucocorticoid hormone

secretion patterns and/or abnormalities in the response to acute stressor exposure may be indicators of these altered profiles. The possibility that symptoms of HPA axis dysregulation could act as useful biomarkers in the clinical setting is also of great interest [1]. A class of polypeptide mediators known as cytokines are traditionally linked to the control of inflammation and immunity. However, in addition to controlling local immune/inflammatory reactions, these peptides also cause a variety of CNS-mediated reactions that go hand in hand with such immune/inflammatory reactions [2]. The mineralocorticoid (MR; type I) and glucocorticoid (type II) receptors have been shown to play a function in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis in rodents. It has been hypothesised that MR is crucial in controlling CRH and ACTH secretion at the nadir of the circadian rhythm because of its extremely high affinity for cortisol [3]. One hormone that can indicate changes in the HPA axis functionality is cortisol, especially in terms of the diurnal cycle [4]. Although the production and action of catecholamines and adrenergic receptors, immunological function, heart contractility, and wound healing all depend on cortisol [5]. There is a growing understanding of the significance of MR in controlling

HPA activity. In the limbic regions of the brain, MR is prevalent and has a strong affinity for the hormones cortisol and corticosterone [6]. Normal growth and organ development depend on the prenatal hypothalamo-pituitary-adrenal (HPA) axis. Recent research, however, suggests that the maturation of the HPA and the subsequent programming of its function can occur throughout foetal life. Glucocorticoid negative feedback appears to be the level of mediation for such change [7].

Pathophysiology of HPA and Associated Syndrome

Chronic stress, Cushing's syndrome, melancholic depression, anorexia nervosa, obsessive-compulsive disorder, panic disorder, excessive exercise (obligatory athleticism), chronic, active alcoholism, alcohol and drug withdrawal, diabetes mellitus, central obesity (metabolic syndrome), post-traumatic stress disorder in children, hyperthyroidism, pregnancy, and hyperthyroidism are all factors that increase the activity of the HPA axis [8]. The relationship between HPA-axis dysfunction and the onset of psychotic disorders was the focus of glucopsychiatric and psychological research on stress, coping, the HPA-axis, the hippocampus, and psychotic disorders [9].

Role of Glucocorticoids & Mineralocorticoids

By interacting with their receptors, Glucocorticoids cause a negative feedback impact on the hypothalamic-pituitary-adrenal (HPA) axis by binding to glucocorticoid response elements on a variety of different genes. Understanding the regulation of the HPA axis has advanced conceptually thanks to the discovery of two distinct glucocorticoid receptors with varied affinity for glucocorticoids [3]. The zona fasciculata of the adrenal cortex is where the hormones known as glucocorticoids are produced. When Adrenocorticotrophic hormone (ACTH) binds to the melanocortin type-2 receptor, a particular cell surface G-protein-coupled receptor, it initiates the production of glucocorticoids (MC2R) [10]. Renin, which is released by the kidneys, transforms angiotensinogen into angiotensin I. Angiotensin-converting enzyme (ACE) then cleaves angiotensin I to produce active angiotensin II. The zone glomerulosa of the adrenals increases synthesis of mineralocorticoids when angiotensin II is present [11]. The hippocampus predominates as the principal site in the brain for type I or mineralocorticoid receptors (MR), which are more confined in their anatomical distribution. Due to the extremely high affinity of glucocorticoids for mineralocorticoid receptors, they are saturated at low glucocorticoid concentrations. It has been suggested that MR activity is

crucial for preserving ACTH inhibition during the cortisol nadir. Studies by Dallman and others have shown that corticosterone levels are low enough and ACTH levels are inversely high enough during the nadir of the circadian corticosterone rhythm to suggest that MR employment could play a crucial role in controlling circadian-driven CRH and ACTH secretion [3].

Multiple acute consequences of GC secretion under stress on the central nervous system (CNS). Studies conducted in vitro, for instance, have shown that GCs prevent glucose from entering neurones. Positron Emission Tomography (PET) evidence of decreased hippocampus glucose uptake is consistent with these findings. The two intracellular receptors known as mineralocorticoid receptor (MR or type I) and dopamine D2 receptor (D2R) combine to mediate the majority of effects in the central nervous system [12].

Utilizing selective receptor antagonists at various points during the circadian rhythm is another strategy for examining the respective contributions of GR and MR in preventing stress and circadian-induced HPA secretion. The research by Ratka et al, Using the intra-cerebro-ventricular injection of the MR antagonist RU 28381 showed that MR was involved in both basal HPA axis secretion and feedback inhibition in response to stress in the mornings (the circadian nadir for rodents). Spironolactone, an MR antagonist, was used in studies by Bradbury et al, on rats, and they discovered that it blocked corticosterone's negative feedback effects on circadian-induced ACTH secretion in both the morning and evenings. As a result, it was determined that MR and GR both contribute to the control of ACTH secretion at the peak and the low points of the circadian rhythm. These investigations were all carried out on rodents, whose primary secreted glucocorticoid, corticosterone, is a more strong MR agonist but a weaker GR agonist than cortisol, the human body's primary glucocorticoid. As a result, it's possible that MR would have a smaller role in actively controlling the HPA axis in humans, where cortisol is the main glucocorticoid, while GR would be primarily responsible for controlling circadian-driven ACTH secretion [3].

When the MR is antagonistic, the HPA axis secretes, with the effect being highest at the nadir of the circadian cycle. Thus spironolactone had any discernible effects on human HPA axis hormone secretion, and if so, whether these effects were seen in the AM, when the HPA axis rhythm is at its highest, or in the PM, when it is at its lowest (the PM) [3].

There is evidence that the hypothalamic-pituitary-adrenal (HPA) axis activity increased during aging. Increased risk for numerous age-related disorders, including diabetes, hypertension, and cardiovascular disease, is linked to elevated glucocorticoid concentrations. Poor sleep and cognitive performance are caused by raised glucocorticoid concentrations. These conditions may also increase the likelihood of serious depression [13].

Adrenocorticotrophic hormone (ACTH) concentrations also increased after cortisol treatment, indicating lower feedback inhibition in older people, according to studies looking at age-related changes in HPA activity. The dexamethasone-suppression test, however, produced conflicting data on the impact of ageing on dexamethasone feedback sensitivity [13]. Corticotropin-releasing hormone (CRH), which is secreted by the hypothalamus in response to stress, causes the pituitary to release adrenocorticotrophic hormone (ACTH). The adrenal cortex releases glucocorticoids in response to ACTH [14].

Transgenic modifications of 11-HSD1 in mice have significant effects on obesity and related metabolic syndrome symptoms. New 11-HSD1 inhibitors may help treat the metabolic syndrome by reducing intracellular cortisol levels, according to promising preclinical data. Glucocorticoids also affect the metabolism and the blood vessel wall [15].

Glucocorticoid feedback mechanisms, which function via two distinct receptor systems at pituitary, hypothalamus, and hippocampus levels, regulate the activity of the HPA axis. The hippocampus is the primary target location for mineralocorticoid receptors (MR), which are confined in their anatomical position. They are already partially saturated at lower basal glucocorticoid levels and have a higher affinity for glucocorticoids than glucocorticoid receptors (GR). In contrast, the GR is extensively distributed in the brain and periphery and has a modest affinity for glucocorticoids. A growing number of GR will become active as brain glucocorticoid levels rise, as they do, for example, during times of stress. Additionally, it is now known that the preceptor metabolism of glucocorticoids by enzymes such as 11 β -hydroxysteroid dehydrogenase (11 β -HSD) also contributes to feedback control, offering an additional level of regulation in particular tissues. The conversion of inactive keto forms of 11 β -hydroxyglucocorticoids and their active forms, such as cortisol in humans, is catalysed by 11 β -HSD. There are two 11 β -HSD isoenzymes, and their functions and tissue

distribution vary greatly. Widespread expression of 11 β -HSD1 in the hippocampus, cerebellum, and neocortex suggests that it may play a role in regulating how glucocorticoids affect mood, memory, and learning. In addition to being located in the hypothalamus and anterior pituitary, 11 β -HSD1 regenerates active glucocorticoids in target cells from the circulating inert 11-keto steroids, indicating a role in neuroendocrine control [13].

The primary Nitric oxide (NO) production enzyme in the hippocampal neuron is called Neuronal nitric oxide synthase (nNOS). The hypothalamus is where corticotropin-releasing hormone is released, which triggers HPA activation in response to stress. As a result, the anterior pituitary gland releases more adrenocorticotrophic hormone (ACTH) [16].

Decreased MR function in the hippocampus, which has been demonstrated to exert an inhibitory influence on HPA activity, may be one explanation for increasing HPA activity during age. The hippocampus has the highest concentration of glucocorticoid and mineralocorticoid receptors in the brain, and there is some evidence that the hippocampus inhibits the HPA axis through MR. Since MR have a strong affinity for cortisol, they are in charge of regulating HPA activity during the evening and early part of the night, when age differences in HPA activity are most noticeable and cortisol is elevated during the circadian nadir. Therefore, it is plausible to suppose that a rise in cortisol levels during that period results from a decreased MR capacity in the hippocampus. As a result, older dogs had lower hippocampus MR levels than younger pups, but not vice versa. Furthermore, it has been demonstrated that blocking MR with spironolactone for 8 days causes aged controls to exhibit an increased rise in HPA activity when compared to young controls. However, a direct comparison is challenging since spironolactone was administered to young and old subjects using various dosages and administration methods. [13]

After pre-treatment with metyrapone at the circadian nadir, fludrocortisone, a mineralocorticoid receptor agonist, exerts a potent inhibitory effect on both ACTH and cortisol. By suppressing the activity of 11 β -hydroxylase, metyrapone crosses the blood-brain barrier and prevents the conversion of the endogenous precursor 11-deoxycortisol to cortisol not only at the adrenal glands but also within the brain. Additionally, it preferentially inhibits the hippocampus's 11 β -HSD1 from functioning, stopping the regeneration of active cortisol. Thus, during the trough of glucocorticoid

secretion, metyrapone further reduces cortisol concentrations in the brain by blocking these two enzymes. Since MR are believed to become mostly depleted as a result, it is possible to study how MR agonists affect the regulation of the HPA axis during [13].

The primary Nitric oxide production enzyme in the hippocampus's MR-Neuronal nitric oxide synthase pathway, Neuronal nitric oxide synthase, mediates the depressed behaviours brought on by stress [17].

Role of cortisol in awakening response (CAR):

Section snippets:

The change from sleeping to waking

As its name suggests, the cortisol waking response is a physiological reaction to awakening (Wilhelm et al., 2007). It is a discrete and unique part of the cortisol circadian cycle, and its properties are not the same as those of cortisol production during the rest of the day (see Clow et al., 2004, Fries et al., 2009). Examining the CAR in relation to other physiological processes that are also started by the CAR seems suitable in order to acquire understanding into potential regulatory influences [18]. One possible explanation for many of the characteristics of depression is abnormal activation of the HPA axis, along with elevated levels of cortisol in the blood, and numerous prior investigations have described a defective HPA negative [19].

Pre awakening influence on cortisol secretion:

Circadian impacts on physiological systems are primarily communicated through the suprachiasmatic nucleus, the body's internal pacemaker (SCN). The SCN, which affects adrenocortical activity through input to the paraventricular nuclei of the hypothalamus, essentially regulates the circadian rhythm of the HPA axis (Buijs et al., 2003, Dickmeis, 2009, Kalsbeek et al., 2006, Krout et al., 2002). These variations in an underlying, considerably quicker ultradian rhythm cause changes in the cortisol secretion patterns.

Post awakening influence on cortisol secretion: the CAR

In one of the rare human investigations that examined neuroendocrine function patterns before and after awakening, both cortisol and ACTH showed a response (Wilhelm et al., 2007). The same study also showed a positive relationship between levels of ACTH and the peak cortisol concentration shortly after awakening, supporting the significance of ACTH signalling (and consequently the HPA axis) for the CAR. There is, however, evidence for additional extra-pituitary input to the CAR, once again.

Relationship between post-awakening cortisol production and patterns of awakening:

There is little direct evidence of the link between patterns of pre- and post-awakening cortisol secretion because the majority of investigations on the CAR are conducted in the home setting. The Wilhelm study from 2007 is a remarkable exception, and it has already been briefly discussed. According to this study, high levels of cortisol release during the night were substantially correlated with a weakened post-awakening increase. Additionally, and in accordance with these results, a substantial.

Inertia from sleep and the CAR:

Sleep inertia is the term used to describe the interval of time between awakening and reaching full alertness. It lasts between 15 and 60 minutes and is characterised by reduced arousal and behavioural performance (Ferrara et al., 2006, Ikeda and Hayashi, 2008). Sleep inertia has observable physiological mechanisms connected to it. For instance, it takes roughly 30 minutes after waking up in the morning to reach global cerebral blood flow velocity values that correspond to the state of **consciousness**.

Evaluation of the CAR:

It is hoped that the data provided here for a potential combination of regulatory mechanisms would stimulate publishing of the two main factors that determine the CAR: the first waking sample (a marker of pre-awakening cortisol secretion) and the dynamic of the increase. Ideally, statistical analysis might be used to examine each of these constituent pieces. Without this knowledge, it will be difficult to identify relationships between the numerous physiological and interesting psychosocial aspects [18].

Role of medicinal plants in HPA axis dysregulation :

The majority of therapeutic plants have anti-depressant properties by regulating synaptic serotonin and dopamine, hypothalamic-pituitary-adrenal axis activity, boosting antioxidant defences, and lowering inflammatory mediators. Through several mechanisms, medicinal plants and their constituents exhibit protective effects against DEPRESSION. The utilisation of medicinal plants as a new source for the creation of antidepressant medications is possible [20].

Agarwood

Aquilaria species (Thymelaeaceae) produce agarwood, a priceless, fragrant non-timber forest product that has been used for ages in Southeast Asia and the Middle East for aromatic, incense, religious, aromatherapy, and medical preparations. One of its most crucial uses is for

medicinal purposes. Agarwood is typically utilised by many peoples in traditional medical systems for a variety of therapeutic purposes. In traditional Chinese medicine, it can reduce pain, stop vomiting, and treat asthma. It has long been used to treat gastrointestinal, neurological, and sedative illnesses in traditional Arabian medicine. It has numerous positive effects, including anti-inflammation, neuroprotection, and anti-depression properties, according to contemporary pharmacological investigations. Agarwood essential oil (AEO) is typically regarded as the primary active component of agarwood, having a variety of pharmacological effects, particularly on brain control. Our most recent research demonstrated that AEO has a sedative-hypnotic action with a putative GABAergic system regulation mechanism. AEO, whose primary active ingredients were benzylacetone, α -gurjunene, and (+)-calarene, was also shown to be able to tranquilize mice by Hiroaki et al. In addition, it has been shown that a variety of AEO-derived chemicals have neuronal activity. For instance, agarofuran was noted to have antidepressant and anxiolytic effects in mice. Buagafuran was shown to be an effective anti-anxiety chemical with low toxicity and a high safety coefficient after a series of agarofuran-like derivatives were synthesised and their activity was evaluated. A promising medication for the treatment of anxiety is buagafuran. Buagafuran is now undergoing phase II clinical studies for the treatment of generalised anxiety. As a result, AEO may be a significant component and a possible source of chemicals that are active against anxiety and depression [21].

Ginseng:

Ginseng has a long history of usage as a medicine in Korea, Japan, China, and the US. Because ginseng includes natural antioxidant components, this long-standing use is possible. These ginsenosides, which are derived from ginseng roots, leaves, stems, and fruit, possess a variety of pharmacological properties. A hundred separate categories make up their breakdown. Ginsenosides have been touted as potent treatments for cell death, immunological disorders, organ damage, and metabolic diseases in numerous research. Additionally, these pharmacologically active components have been demonstrated to boost synaptogenesis, neuronal development, neurotransmission, and neurogenesis, supporting the central nervous system's defence against unexpected occurrences. Ginseng is also said to be effective for enhancing memory. As a tonic and a

rejuvenator, ginseng has been utilised as an adaptogen to cure disease [22].

Asparagus racemosus

The plant *Asparagus racemosus* (AR), a significant food and medicinal plant, is categorised as an adaptogen. Despite the fact that AR is frequently used in foods and nutraceuticals. Its effectiveness has only been studied in relation to experimental disorders. Its goal was to determine the impact of standardised AR methanolic extract (MAR) on experimentally unaltered animals in order to determine the effects on stress pathways [23].

Gastrodiae rhizome:

In an effort to create alternative therapies to lessen the clinical symptoms of depression, many functional foods and herbal remedies are gaining popularity. The dried rhizome of *Gastrodia elata* Blume, a member of the Orchidaceae family, is known as *Gastrodiae rhizoma* (GR). It has been used for millennia as both a traditional Chinese medicine and a functional food to treat a variety of illnesses, such as headaches, vertigo, convulsions, paralysis, rheumatism, and lumbago [24].

Hypericum perforatum:

We investigated the potential modulatory effects of *Hypericum perforatum* plant extract (commonly known as St. John's Wort), a medicinal herb used to treat mild depression symptoms. Adrenocorticotrophic hormone (ACTH) and corticosterone levels in circulating plasma were considerably reduced in male Sprague-Dawley rats given chronic imipramine treatment (daily injections for 8 weeks). Even at the highest doses examined, chronic St. John's Wort therapy (daily gavage for 8 weeks) showed no impact on plasma levels of corticosterone or ACTH. Our findings support earlier research suggesting that imipramine may have notable peripheral HPA axis-mediated effects. Our data, however, do not support *Hypericum perforatum*'s involvement in altering HPA axis function, indicating that alternate mechanisms may be used to mediate its antidepressant effects [25].

Conclusion

The regulation of the HPA axis is a highly complex process that is influenced by both positive and negative feedback loops. Many mediators, including hormones, neurotransmitters, cytokines, or growth factors, have an impact on the functions of HPA axis. Glucocorticoids are crucial for maintaining homeostasis and allowing the body to anticipate, react to, and recover from physical and mental stress. The imbalance between GR and MR may be a contributing factor in the dysregulation of the HPA axis. Although few research

have examined the activity of MRs in depression, evidence has repeatedly shown that GR function is compromised in major depression leading to a reduction in GR-mediated negative feedback on the HPA axis. A preventive effect against depression is demonstrated by medicinal plants and their constituents through various possible mechanisms. Antidepressant drug research can find new inspiration from medicinal plants.

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