# NEUROENDOCRINE: THE HYPOTHALAMUS-PITUITARY-ADRENAL AXIS AND THE RELATION TO STROKE

**Rr. Fitria Dwi Intan Milleniari[1], Kadek Putri Devyanthi Rahayu[2], Luh Putu Lina Kamelia[3]**

[1,2,3]Prodi Kedokteran, Universitas Pendidikan Ganesha

e-mail : rr@undiksha.ac.id, putridevyanthi19@gmail.com, kamelia.lina@gmail.com

**Abstrak**

Glukokortikoid merupakan komponen esensial yang berfungsi untuk menjaga homeostasis dan menyiapkan individu dalam merespon serta memanajemen stress fisik maupun emosional. Kortisol yang merupakan glukokortikoid, disintesis oleh korteks adrenal melalui jalur aksis hipotalamus-pituitari-adrenal (HPA Axis). Jalur HPA Axis merupakan jalur yang mana hipotalamus dapat menerima sinyal terhadap perubahan lingkungan eksternal serta internal dan kemudian akan menghasil suatu respon umpan balik. Gangguan pada jalur HPA Axis dapat mengganggu keseimbangan homeostatik organisme (stresor), yang kemudian direspon dengan melepaskan *corticotropin-releasing hormone* (CRH) dan *arginine vasopressin* (AVP) dari nukleus paraventrikular. CRH dihasilkan melalui kelenjar pituitari anterior yang kemudian merangsang pengeluaran *adrenocorticotropic hormone* (ACTH) sehingga menghasilkan kortisol. Respon tubuh terhadap adanya stresor akan berdampak pada teraktivasinya sistem saraf simpatik. Keadaan tersebut dapat memiliki resiko terhadap stroke. Meningkatnya glukokortikoid menyebabkan peningkatan sel inflamasi sehingga hal ini menyebabkan disregulasi HPA axis yang akan menyebabkan inflamasi iskemik pada vaskularisasi otak. Kortisol dikatakan menjadi salah satu biomarker dalam menentukan prognosis stroke iskemik..

**Kata Kunci**: Aksis HPA, Respon stress, Stroke

**Abstract**

Glucocorticoids are essential components to maintain homeostasis and prepare individuals to respond and manage physical and emotional stress. Cortisol, which is a glucocorticoid, is synthesized by the adrenal cortex via the hypothalamic-pituitary-adrenal axis pathway. The HPA Axis pathway is a pathway where the hypothalamus can receive signals to changes in the external and internal environment and then generate a feedback response. Disturbances in the HPA Axis pathway can disrupt the homeostatic balance of the organism (stressor), which then responds by releasing corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the paraventricular nucleus. CRH is produced through the anterior pituitary gland which then stimulates the release of adrenocorticotropic hormone (ACTH) to produce cortisol. The body's response to the stressor will have an impact on the activation of the sympathetic nervous system and have a risk relationship to stroke. Increase of glucocorticoid causes an increase in inflammatory cells so this causes HPA axis dysregulation which will cause ischemic inflammation in the brain vascularization. Cortisol is said to be one of the biomarkers in determining the prognosis of ischemic stroke.

**Keywords:** HPA Axis, Stress Response, Stroke

## INTRODUCTION

In order to maintain survival, individuals have their challenges in responding to environmental influences. This response is referred to as the "stress response" which is the body's reaction related to the stressor (agents that trigger the activation of the stress response). The stress response becomes a real threat to homeostasis and individual well-being which results in the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis system. The HPA axis is a complex neuroendocrine system that functions in the physiological regulation of homeostasis and response to homeostatic threats. HPA axis activation will provide the primary hormonal response to homeostatic threats due to various types of stressors. This reaction will trigger the secretion of glucocorticoid hormones that will work on multiple organ systems to channel energy resources in order to meet the actual or reserved needs of the target organs[(1)].

Considering from the anatomical structure, the HPA axis is represented by the pituitary gland which is located inside the head at the base of the skull and in the opening of the sphenoid bone surrounded by the optic chiasma, its blood vessels and other important brain structures. The pituitary gland or hypophysis gland is divided into the adenohypophysis anteriorly and the neurohypophysis or posterior lobe. Adenohypophysis consists of three parts, namely pars distalis (anterior lobe or pars glandular), pars intermediate (intermediate lobe), and pars tuberalis (pars infundibular). The neurohypophysis originates from the development of the brain and also consists of three parts namely the infundibulum, pituitary stalk, posterior lobe or pars nervosa[(2)].

Disruption of pathways and feedback mechanisms in the HPA axis can lead to long-term changes in the synthesis of neuropeptides and neurotransmitters in the central nervous system and the synthesis of glucocorticoid hormones in the periphery system. This can potentially cause disruptions in the neuroendocrine function, behavior, autonomic function, brain vascularization and metabolism[(3)]. The excessive or deficiency of hormone production will cause an imbalance that will trigger several interference from the endocrine system. Therefore, an understanding of the physiology of the HPA axis and its regulation and the relation to stroke emergence needs to be reviewed in more depth within this reference.

## DISCUSSION

The hypothalamus is located at the base of the brain, specifically under the thalamus. The hypothalamus is part of a vital organ that looks like an almond and weighs about 4 grams. The hypothalamus plays an important role in performing many functions that are essential for survival. The hypothalamus is part of the limbic system, which is the area of the brain that is composed of the thalamus, amygdala, hippocampus, and cingulate gyrus. The limbic system is involved in emotional response, long-term memory, olfactory function and the acquisition of new skills, and contributes to a variety of behavioral responses. The hypothalamus is said to be the thermoregulatory center that regulates body temperature, fluid balance, blood pressure regulation, and the sensations of thirst and hunger. The hypothalamus is connected directly to the pituitary gland by a thin rod called the infundibulum. Some actions initiated by the hypothalamus are mediated through secretions produced by the pituitary gland[(2)].

The pituitary gland, also known as the hypophysis gland, is a pea-sized structure located in the ventral part of the cerebrum and is connected to the optic nerve at the front of the cerebral and the hypothalamus via the infundibular (Figure 1). The pituitary gland is protected by the fossa Sella Turcica, the base of the sphenoid bone, and is attached to the periosteum by the Meninges. The pituitary gland is divided into an anterior portion called the adenophysis and a posterior portion called the neurohypophysis. Adenophysis originates from the embryonic epithelial tissue of the oral

cavity, which makes up nearly 70-80% of the pituitary gland. The adenophysis is composed of the pars distalis (in the form of a large lobe) and the pars tuberalis (contains vascularization covering the infundibulum), while the neurohypophysis has a network of nerves that innervates from the hypothalamus through the infundibulum and pars nervosa. The two pituitary glands are then separated by the pars intermedia and the Rathke's cleft which emerges from the palate of the oral cavity during embryonic development. Failure in the development of the embryo to form Rathke's cleft will have an impact on the abnormal structure of the pituitary gland [(4)].

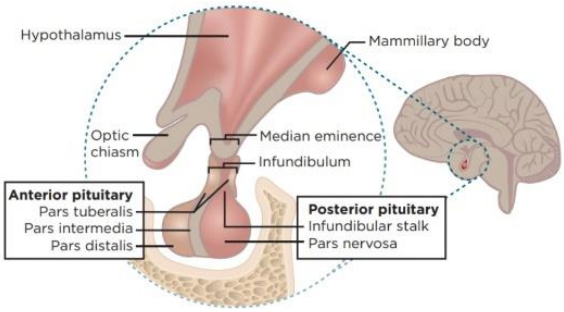


Figure 1. Anatomy of Pituitary Gland (Sherwood, 2010)

The human body has two adrenal glands which are located on top of each kidney in a fat capsule. Each adrenal gland consists of a cortex which produces steroids and a medulla which produces catecholamines[(5)].

The adrenal cortex produces three types of steroids: mineralocorticoids (aldosterone) which affect electrolyte balance especially Na and K; glucocorticoids (cortisol) which play a role in the metabolism of glucose, protein, and fat in adaptation to stress; and sex hormones (dehydroepiandosterone) that produce androgens for men, and estrogens for women[(5)].

The adrenal medulla is a modified part of the sympathetic nervous system. It is composed of preganglionic neurons originating in the central nervous system that have axonal fibers that terminate in second postganglionic neurons located peripherally and then terminate in effector organs. The neurotransmitter released by sympathetic postganglionic fibers is norepinephrine, which interacts with the organs innervated by binding to adrenergic receptors. Like sympathetic fibers, the adrenal medulla secretes norepinephrine, but its principal secretory product is epinephrine. Both epinephrine and norepinephrine belong to the class of catecholamines, which are derived from the amino acid tyrosine. Epinephrine and norepinephrine are synthesized almost entirely in the cytosol of the secretory cells of the adrenal medulla. Once produced, these catecholamines are stored in chromaffin granules, which are similar to transmitter storage vesicles in sympathetic nerve endings[(5)].

Activation of the HPA axis begins with the production of CRH. CRH plays an important role in maintaining homeostasis. Nerves that produce CRH are located in the paraventricular (PVN) in the hypothalamus which route to the external layer of the hypothalamus (*median eminence*) thereby releasing CRH into the portal hypophyseal circulation. Some of the CRH hormone-producing nerve pathways in the PVN also spread to noradrenergic pathways in the brainstem, descending pathways of the cortex and limbic system (septum-amygdala-hippocampus)[(6)].

Cortisol secretion by the adrenal cortex is regulated by a negative feedback system involving the hypothalamus and anterior pituitary (Figure 2). ACTH from the anterior pituitary acts via the cAMP pathway which stimulates the adrenal cortex to secrete cortisol. The negative feedback system for cortisol maintains relatively constant levels of CRH hormone secretion in the anterior pituitary and hypothalamus. In the negative feedback control, there are two additional factors that affect plasma cortisol concentrations, namely diurnal rhythm and stress, both of which act on the hypothalamus to change the level of CRH secretion[(6)].

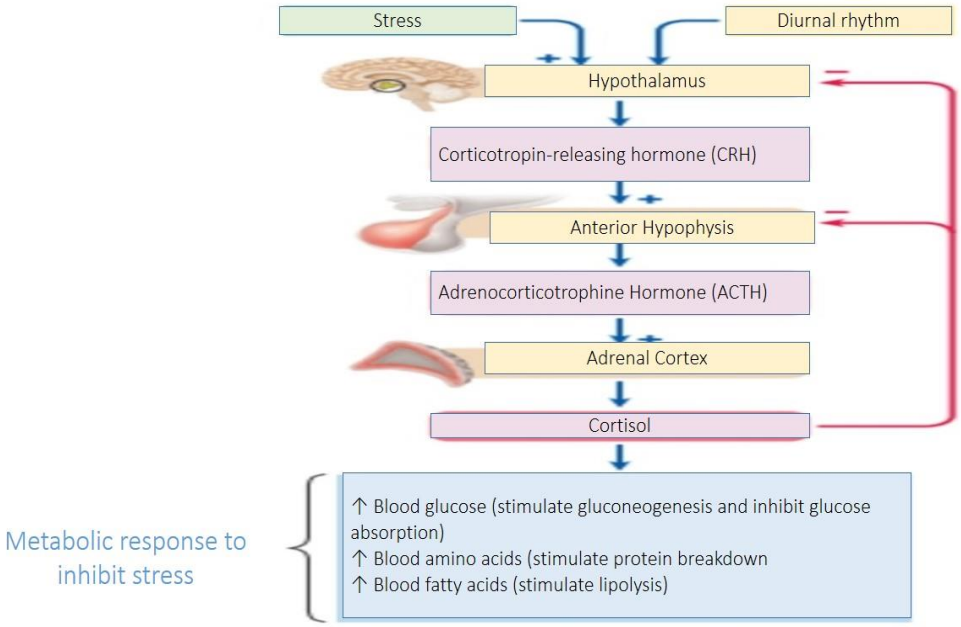


Figure 2. Cortisol Secretion Control (Sherwood, 2010)

CRH acts exclusively on the CRH-R1 receptor in the anterior pituitary to stimulate ACTH biosynthesis and secretion from cellular stores. CRH in stimulating ACTH secretion is caused by AVP which is produced by PVN. AVP by itself has a weak effect on ACTH release. The release of ACTH into the peripheral circulation stimulates the adrenal cortex to release glucocorticoids (cortisol). HPA axis regulation is governed by positive and negative feedback. It is influenced by several mediators such as hormones, neurotransmitters, cytokines, and growth factors. Glucocorticoids are the end product of the HPA axis which has a function to maintain homeostasis and enable individuals to prepare for, respond to, and cope with physical and emotional stress[7].

The hypothalamus-pituitary-adrenal axis is a complex system of neuroendocrine systems that are linked to the sympathetic nervous system, the brain and peripheral functions of the body. The HPA axis has an important role in responding to stressors (physical or psychological) that disrupt homeostasis. Various stressors can elicit some specific responses that are typical (Figure 3) for that stressor; for example, specific body responses to exposure to cold are shivering and skin vasoconstriction, while specific responses to bacterial invasion include increased phagocytic activity and antibody production. When a stressor is identified, a nervous and hormonal response arises that takes defensive actions to deal with an emergency. This response involves interactions between hormones and the central nervous system[8]

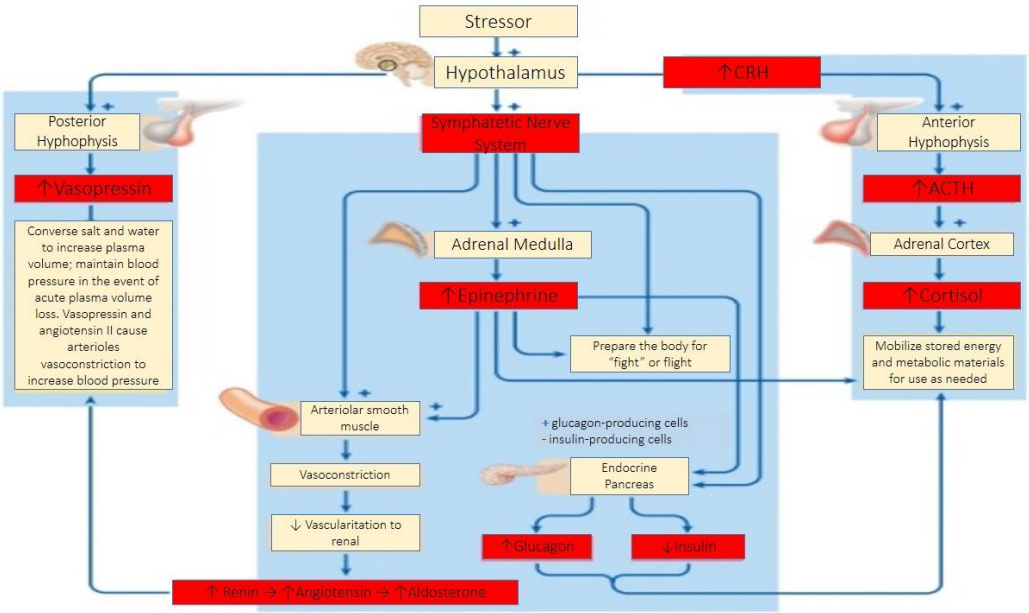


Figure 3. The HPA Axis Response to Stress (Sherwood, 2010).

The components involved in the stress system are CRH (*corticotropine releasing hormone)*, AVP *(arginine vasopressin)*, norepinephrine and the central sympathetic system in the brainstem. This is a series of activation of the HPA axis, the sympathetic nervous system, and the systemic adrenomedullary as a peripheral pathway of the stress system[(9)].

The nervous response to stressful stimuli is the activation of the symphatetic nervous system (Figure 4). . The sympathetic system activates hormone reinforcement in the form of epinephrine hypersecretion from the adrenal medulla. Epinephrine strengthens the sympathetic response and mobilizes stored carbohydrates and fats. Activation of the stress central system can also stimulate the sympathetic and adrenomedullary nervous systems affecting the secretion of catecholamines and some neuropeptides.

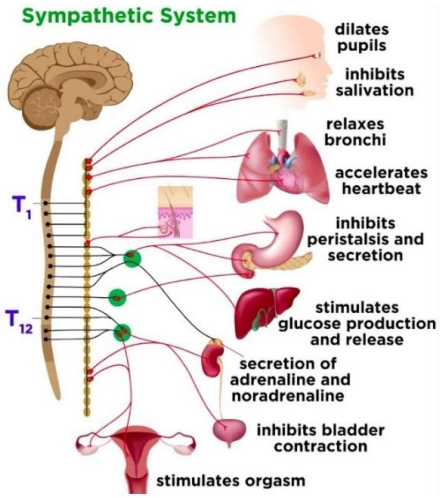


Figure 4. Sympathetic nervous system (Sherwood, 2010)

The stress system can also be activated at rest, responding to different signals (circadian and neurosensory via the circulatory and limbic systems). Activation of the stress system can increase arousal, accelerate motor reflexes, increase attention and cognitive function, reduce appetite and sexual arousal, and also increase pain tolerance[(1)]. Judging from this process, under stress conditions a mechanism of glucocorticoid secretion by the adrenal cortex also occurs as a defense response of the body. The body's defense response

is not to protect itself from the source of stress itself, but to normal defense reactions activated by stress. Glucocorticoids are produced by inhibiting these defense reactions, thereby preventing excessive body responses that threaten homeostasis[10].

The HPA axis as the neuroendocrine system that responds to a stressor will provide an acute stress response, one of which has a relationship with the incidence of stroke. Based on epidemiological data, CRF (*Corticotropin Releasing Factor)* is a neuropeptide that mediates acute neurovascular damage[11]. In diabetics, the state of increased blood sugar and dysfunction of insulin is a stressor that causes dysregulation of the HPA axis so it can trigger stroke exacerbations due to vascular inflammation. The relationship between HPA dysfunction and the incidence of stroke has been proven through animal studies in which vascular inflammation was accompanied by increased CRH levels [12].

Glucocorticoids as the end result of the HPA axis are actually anti-inflammatory mediators, however, several studies suggest that glucocorticoids can act as pro-inflammatory mediators in central nervous system damage. The increase in glucocorticoids causes an increase in inflammatory cells (granulocytes and macrophages), IL-1b, and TNF-a. Increased glucocorticoids and dysregulation of the HPA axis will lead to ischemic inflammation in the brain vascularization[12]. In addition, cortisol which is a glucocorticoid hormone is also said to be a biomarker in determining the prognosis of ischemic stroke[13].

Glucocorticoids released during activation of the HPA axis are implicated in stroke-induced brain dysfunction. Research shows that damage after stroke is not limited to the infarct area, but also spreads to areas of the brain that are not experiencing ischemia and causes secondary damage and often occurs in areas far from the infarct zone[14].

Although brain damage caused by ischemic stroke primarily affects the cerebral cortex, it has been hypothesized that the essential mechanism of cognitive impairment and depression induced by ischemic stroke is to a large extent related to the hippocampus. The abundant adrenal stress hormones glucocorticoids in the hippocampus are essential for the physiological control of various executive functions and the behavioral responses that normally represent adaptive reactions. Hippocampal receptor-mediated signal transduction of glucocorticoids regulates genomic activation that underlies neuroplasticity and behavioral adjustment to stressogenic factors. Milot and Plamondon (2011), demonstrated increased sensitivity and responsiveness of the HPA system at long intervals after cerebral ischemia in rodents. These effects contribute to post-ischemic cognitive impairment (disturbances in spatial memory) and hippocampal degeneration[15].

In addition to post-stroke cognitive and emotional disturbances, stroke can also trigger epileptogenesis, which is often followed by depression. Common molecular and cellular mechanisms of this comorbidity include remote hippocampal damage associated with dysfunction of the HPA axis, glucocorticoid receptors, development of neuroinflammation, leading to neurodegeneration and loss of hippocampal neurons and aberrant neural network formation. The mechanisms of glucocorticoid-mediated hippocampal damage include alterations in subgranular neurogenesis. These disorders contribute to cognitive and emotional disturbances and epileptogenesis[16].

## CONCLUSION

The hypothalamic-pituitary-adrenal axis pathway synthesize cortisol (glucocorticoids). Glucocorticoids are essential components to maintain homeostasis and prepare individuals to respond and manage physical and emotional stress. The body's response to the stressor will have an impact on the

activation of the sympathetic nervous system and have a risk relationship to stroke. The increase in glucocorticoids causes an increase in inflammatory cells (granulocytes and macrophages), IL-1b, and TNF-a. Increased glucocorticoids and dysregulation of the HPA axis will lead to ischemic inflammation in the brain vascularization. In addition, cortisol which is a glucocorticoid hormone is also said to be a biomarker in determining the prognosis of ischemic stroke

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