บทฟื้นฟูวิชาการ ■ Review Article

ผลของความเครียดและคอร์ติซอลต่อหน้าที่ด้านพฤติกรรมของสมอง: อารมณ์ และความจำ

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Effects of Stress and Cortisol on the Brain Behavioral Functions: Mood and Memory

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คอร์ติซอล หรือที่รู้จักกันว่าเป็นฮอร์โมนแห่งความเครียด มีผลควบคุมการทำงานของระบบต่างๆของร่างกาย ทั้งระบบประสาท ระบบหัวใจหลอดเลือด ระบบกระดูกกล้ามเนื้อ ระบบหายใจ ระบบต่อมไร้ท่อ และระบบขับถ่ายปัสสาวะ ระบบประสาทจัดเป็นระบบที่มีความสำคัญในการควบคุมระดับคอร์ติซอล เพื่อควบคุมหน้าที่การทำงานของร่างกายให้เป็นปกติ คอร์ติซอลยังมีบทบาทสำคัญในการควบคุมการเผาผลาญของร่างกาย การตอบสนองต่อความเครียด การสร้างวงจรสัญญาณประสาท การหลั่งของสารสื่อประสาท ซึ่งส่งผลต่อการตอบสนองทางอารมณ์และความจำ บทความปริทัศน์นี้ได้สรุปความรู้ใหม่เกี่ยวกับผลของคอร์ติซอลต่อหน้าที่ด้านพฤติกรรมของสมองทางด้านอารมณ์และความจำ รวมถึงให้ข้อมูลเกี่ยวกับการหลั่งคอร์ติซอลที่ถูกชักนำโดยความเครียด ผลของคอร์ติซอลต่อการทำงานของอวัยวะต่างๆ โดยเฉพาะสมอง บทความปริทัศน์นี้ได้อภิปรายผลของระดับคอร์ติซอลที่ผิดปกติต่อความผิดปกติทางสติปัญญาและอารมณ์ รวมถึงความผิดปกติของระดับคอร์ติซอลจะส่งผลต่อการเพิ่มความเสี่ยงของการเกิดโรคทางจิตประสาท และโรคความเสื่อมทางระบบประสาท ท้ายบทความนี้กล่าวถึงกลยุทธ์ในการบรรเทาความเครียด เพื่อการพัฒนาด้านอารมณ์และความจำ

คำสำคัญ: คอร์ติซอล, ความเครียด, สมอง, อารมณ์, ความจำ

Cortisol, also well-known as the stress hormone, has various effects on physiological functions of the body systems including the nervous, cardiovascular, musculoskeletal, respiratory, endocrine, and urinary systems. The nervous system has an important role in the regulation of cortisol levels for controlling normal body functions. Cortisol also plays crucial roles in the metabolic control of body functions, stress reaction, neuronal circuit formation, neurotransmitter modulation, and regulation of mood and memory. This review article summarizes new information of the effects of cortisol on behavioral brain functions, mood and memory, and provides information on stress-induced cortisol secretion and actions of cortisol on various organs, especially the brain. This review also discusses the effects of abnormal cortisol levels on cognitive and mood disorders, as well as the abnormality of cortisol levels which increases risks of the neuropsychological and neurodegenerative diseases. Finally, the article provides information on strategies to relieve stress for improving mood and memory.

Keywords: Cortisol, Stress, Brain, Mood, Memory

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Introduction

Stress-associated mental illness is believed to be a major factor for the development of physical health problems. According to the World Health Organization (WHO), mental disorders are possibly the number one factor causing disability worldwide, particularly in people aged between 15 and 44.[1] Stress is defined as mental state or emotional strain caused by injurious situation and trouble life. Stress influences the activity of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system (ANS), and immune system that promote psychological and physiological alterations.[2] The stress response is associated with increased hormonal secretions comprising of cortisol, catecholamine, growth hormone, and prolactin, the effects of which lead to enhanced energy metabolism and behavioral activation.[3] Among these hormones, cortisol is well-recognized as the hormone closely associated with emotional stress, cognitive performance, structural brain volume and function.[4-5] The abnormality of cortisol levels is related to clinical correlation among patients with Cushing's syndrome, adrenal insufficiency (Addison's disease), severe sepsis, depression, anxiety, stroke, and Alzheimer's disease.[4-7] The clinical and research studies frequently use cortisol as an indicator for diagnosis and monitoring the treatment of patients. To evaluate the HPA axis activity, the cortisol levels are usually determined in serum, plasma, saliva, urine, and hair.[8-9] Hence, cortisol, a biological marker of stress response, has been investigated in various sample types for prediction of the disease risks.

Cortisol is a steroid hormone in the group of glucocorticoids. It is secreted from adrenal gland and transported to the brain, and has many effects on the central nervous system (CNS). The brain is recognized as the site of cortisol action and is responsible for alterations of mood and cognition.[10] Patients with high cortisol levels, particularly with Cushing's syndrome, often show cognitive dysfunction and mood disorder. However, the opposite effects can also be observed during moderate cortisol levels.[11] In the brain, the receptors for cortisol are expressed in the prefrontal cortex (PFC), hippocampus, and amygdala.[12] The PFC is part of the cerebral cortex covering the front of the frontal lobe. The function of the PFC involves thinking, planning, decision making, and executive function. The hippocampus is part of the limbic system, and plays a key role on storing and retrieving of episodic and spatial memories. The amgydala is the limbic region responsible for processing and perceiving emotional information.[12-13] Stress-induced cortisol release also modulates neuronal circuits, synaptic support, dendritic arborization, and neurotransmitter modulation, as well as mood and memory.[14] Therefore, cortisol levels in the blood and in the brain are used to estimate emotional, cognitive, and physiological states, along with risks of the diseases. This review article gives information on experiments and clinical studies that have reported novel functions of cortisol in several brains regions related to mood and memory. Moreover, the article provides information on the strategies for reducing stress, improving emotion, and cognition.

1. The regulation of cortisol secretion, stress response, and physiological actions of cortisol

Cortisol is produced mainly by the zona fasciculata layer of the adrenal cortex. Cortisol release is under the regulatory control of the HPA axis. It is classified as a member of steroid hormones and is synthesized from cholesterol under the influence of adrenocorticotropic hormone (ACTH). The regulation of cortisol secretion is controlled by physical and emotional stress, and also blood glucose levels. Stressful situations activate the HPA axis which stimulates the release of corticotrophin releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus (PVH). Then, CRH promotes ACTH, the secretion from the anterior pituitary gland. In turn, ACTH triggers cortisol release from the adrenal gland.[15] Cortisol circulates into a bloodstream, mainly as protein-bound cortisol. Some cortisol, however, circulates as free cortisol or its metabolites. In the brain, cortisol passes through the blood brain barrier (BBB) and binds with its receptor to regulate mood and memory.[16] Additionally, cortisol affects the bone and skin, and activities of the heart, kidney and liver. The physiological functions of cortisol play a central role in various homeostasis maintenance mechanisms. The regulation of cortisol secretion and physiological function of cortisol in various organs are shown in Figure 1. For the brain, an excess cortisol induces neuronal dysfunctions that affect mood, memory, and cause behavior alteration.[17] For the skin, cortisol inhibits fibroblast proliferation and causes decreasing of collagen synthesis leading to the thinning of skin.[17] For the bone, cortisol inhibits osteoblast activity, and thus reduces new bone formation. For the heart, cortisol helps to sustain blood pressure by maintain-

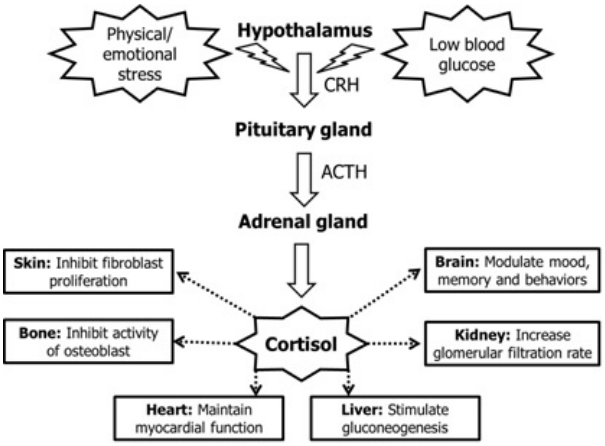

Figure 1 Stress-induced cortisol secretion controlled by the hypothalamic-pituitary-adrenal (HPA) axis. The diagram shows the physiological functions of cortisol in various organs.

ing cardiac function. For the kidney, cortisol increases glomerular filtration rate (GFR) by enhancing glomerular blood flow.[17] For the liver, cortisol regulates glucose synthesis (gluconeogenesis) in our metabolism system.[17]

2. Effect of cortisol on the brain glucocorticoid receptors for controlling memory and mood

Cortisol exerts cognitive function through two types of receptors, mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). Interestingly, MRs show higher affinity for glucocorticoids, mainly cortisol, than GRs. These receptors are found in several brain regions.[7,15] The hippocampus regulates episodic memory, expressed on both MRs and GRs. The PFC, on the other hand, mediates executive function, expressed only on GRs. The amygdala also exhibits arousal and emotional states, mostly expressed on MRs. MRs are related to enhancement effects, but GRs are associated to inhibitory effects.[7,15] In the hippocampus, moderate levels of cortisol stimulate MRs with higher affinity resulting in cognitive enhancing effects.[7,15]As cortisol levels increase, the enhancing effects are still maintained for MRs activity until MRs are saturated. Furthermore, when cortisol levels continue to increase, GRs are increasingly stimulated, leading to negative effects on the memory.[15-16] In the PFC, elevated cortisol levels can impair executive function. Low cortisol levels, on the other hand, worsen cognitive function.[7,15-16] In the amygdala, elevated cortisol levels during stressful event have been found to increase amygdala response to emotional stimuli in healthy volunteers.[17] The cognitive decline and negative mood are commonly found in patients with abnormal cortisol levels due to adrenal gland dysfunction in both Cushing's disease and Addison's disease.

3. Effects of stress on the brain behavior functions

3.1. The brain is vulnerable when exposed to stress-induced cortisol secretion

The communication between the brain and body is regulated by neuroendocrine system through hormones that control body functions. The hippocampus is the brain area susceptible to chronic stress. This part of the brain plays a key role for structural and functional plasticity.[18] The hippocampus also provides interconnections to the amygdala and PFC for controlling emotional memory.[12] These brain regions contain steroid hormone receptors, both MRs and GRs. Previous studies have shown that cortisol has effects on behavioral arousal and object recognition memory mediated via MRs and GRs in the hippocampus and amygdala.[13] Cortisol is necessary for an effective stress response, but its overproduction can cause hippocampal degeneration by inducing structural and functional dysfunctions.[18] Moreover, stress-induced elevation of cortisol exacerbates hippocampal damage caused by neurotoxins and metabolic challenges.[18] An experiment in mice showed that mice exposed to stress paradigms (loud noise, hours-long light, jostling, and restraint) were impaired in novel object recognition after such multimodal stresses, and showed a reduced number of synapses in hippocampal Cornu Ammon 1 (CA1) and Cornu Ammon 3 (CA3) regions.[19] Furthermore, hippocampal connectivity with septum and thalamus was reduced in multimodal stresses. However, hippocampal connectivity with the amygdala increased when compared with prolonged restraint.[19] The amygdala has a pivotal role in mental disorders and is highly responsive to stressful event. This brain area contains a moderate number of glucocorticoid receptors and responds to glucocorticoid synthesis. Acute stress causes impaired dendritic spine formation in basolateral amygdala neurons.[20] The PFC is a sensitive area to the deleterious effects of stress exposure.[21] This brain region shows neuronal structural and functional plasticity due to neuronal circuit alteration, caused by altered neurochemistry. Stress affects dendritic arbor and synaptic numbers in many brain regions including the hippocampus, amygdala, and

PFC.[21] Stress also affects cognitive function, emotional regulation, and behavior as well as neuroendocrine and autonomic functions.[21] Chronic stress causes shrinkage of dendrites in the PFC and hippocampus, but causes expansion of dendrites in the basolateral amygdala (BLA).[22] Hence, these brain regions are vulnerable to chronic stress due to brain structural and physiological dysfunctions. The structural and functional plasticity of the brain regions influence behavioral alterations. These alterations are related to changes in the neurochemistry within the neural pathways that control brain behavioral functions.

3.2. Endogenous cortisol transports across blood brain barrier

The blood brain barrier (BBB) is the structure that separates CNS from the peripheral nervous tissues. The BBB consists of cerebrovascular endothelial cells connected via tight junctions. These junctions are normally impermeable to bacteria, viruses, and toxins, but are selectively permeable to steroid hormones such as cortisol, estrogen, testosterone and so forth. Because these hormones are small and lipophilic, they can pass through the brain by bidirectional and non-saturable processes allowing rapid equilibrium within the brain.[23] Acute stress causes an increase in plasma cortisol which rapidly passes through the BBB which circulates to reach receptors located in the cerebral cortex, limbic system, hippocampus, amygdala, thalamus, and hypothalamus. The binding of cortisol to both MRs and GRs on these brain regions regulates behavior, cognition, emotion, and motivation.[24-27] Stress activates the release of cortisol which passes through the BBB and modulates neurotransmitter release in the limbic region for regulation of mood and memory. The processes are demonstrated in Figure 2.

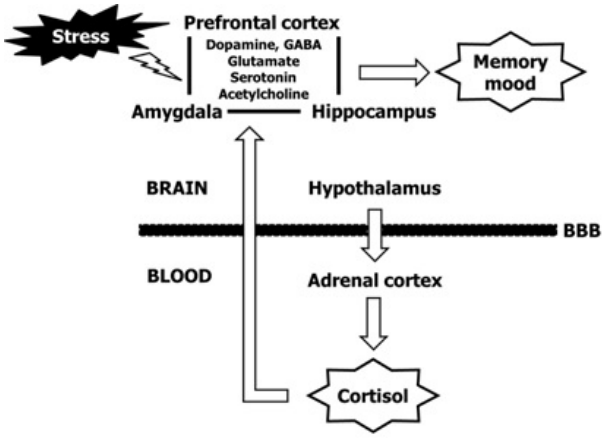

Figure 2 Activation of cortisol release by stress. Cortisol passes through blood brain barrier to feedback within the brain. Cortisol plays a key role in modulating neurotransmitter release in the limbic regions of the brain (prefrontal cortex, hippocampus, and amygdala), which in turn affects the regulation of mood and memory.

3.3. Influences of stress on neurotransmitter modulation

3.3.1 Dopamine (DA)

Dopaminergic neuronal circuits normally accumulate in midbrain regions including substantia nigra (SN) and ventral tegmental area (VTA). The dopaminergic neurons send the nerve signal to the PFC, hippocampus, entorhinal cortex, amygdala, and striatum. Groups of neurons play major roles on mood, behavior, and influence on learning processes for behavioral reinforcement.[28] Stress activates the HPA axis to regulate cortisol secretion. Elevated cortisol levels are the main factor to control dopamine signaling in both the PFC and striatum.[29] Psychological stress stimulates PFC dopamine release in early adulthood.[30] Such stress also decreases working memory and attention related to PFC dopaminergic neuronal activity.[31,32] Chronic stress affects PFC dopaminergic neuronal function and dopamine-related behaviors by decreasing basal dopamine levels and dopamine receptor 2 (DR2) expressions. Chronic stress also reduces dopamine transporters and causes gene expression of monoamine oxidase A (MAO-A) to increase.[33,34] The function of dopamine in the striatum changes during stress response. The mechanism is related to increasing in DR1 binding and aggregation which result in anxiety-like behavior in rats.[33,34] Therefore, stress influences the brain dopamine synthesis, dopamine receptor, dopamine transporter, and dopaminergic neuronal functions involved with mental, cognitive, and behavioral disorders.

3.3.2 Glutamate

Glutamate, an excitatory amino acid, plays a crucial role in both adaptive and destructive effects on brain stressors. Glutamate is responsible for producing the excitatory postsynaptic potential (EPSP) in the cerebral cortex. Coupling of glutamate with NMDA receptors mediates synaptic transmission that controls neuronal function in the PFC for working memory regulation. Dysfunction of glutamatergic

transmission is considered as pathology of stress-related mental disorders with impaired working memory.[35] Cortisol is an essential hormone for glutamate release in the cortical and limbic systems including the PFC, hippocampus, and amygdala.[36,37] Acute stress enhances glutamatergic transmission in the hippocampal CA1 region which is regulated on MRs and GRs.[38] Stress affects synaptic plasticity via efficacy of glutamatergic neurotransmission in the PFC and hippocampus.[13] Moreover, acute stress inhibits long-term potentiation (LTP) in the amygdala and PFC pathway, and leads to hippocampal LTP impairment.[39] Chronic stress also reduces LTP in the thalamus and PFC pathways, and impairs connections between the hippocampus and PFC.[40,41] The interruption of these pathways is related to the PFC dependent tasks, which are involved in working memory and behavioral functions.

3.3.3 Serotonin (5-HT)

Serotonin (5-HT) affects behaviors and emotions. In the brain, 5-HT is synthesized from L-tryptophan in serotoninergic neurons, located within the raphe nuclei.[42] Serotonin plays a key role for regulation of cortisol release. Increasing 5-HT raises plasma cortisol level whereas depletion of 5-HT precursor or 5-HT transporter reduces cortisol levels.[43] It is found that the regulation of hypothalamic CRH release is controlled by serotonergic neurons from the raphe nuclei.[44] Heisler and colleagues reported that 5-HT stimulates CRH signaling systems via the activation of serotonin 2C receptors (5-HT2CRs) in the PVH.[45] Thus, the serotonergic neurons are important in the HPA axis regulation during stressful events. The reduction of 5-HT precursors causes cortisol levels to increase, and can be related to the development of affective disorders such as depression and anxiety.

3.3.4 Acetylcholine (ACh)

The cholinergic neurons in the CNS use ACh as neurotransmitters. These neurons are located at the hippocampus, PFC, amygdala, and striatum. These brain regions play major roles in adaptation and response to stress.[46] Impairments of these brain regions cause depression and cognitive dysfunction.[46] The hippocampus, PFC, and amygdala receive strongly cholinergic input from basal forebrain.[46] ACh commonly improves cortical sensitivity to external stimuli, reduces corticocortical communication, and increases attention.[47] However, increases in ACh signaling can result in symptoms related to depression and anxiety.[47] Stress-induced ACh release can lead to adaptive responses to environmental stimuli. Also, prolonged elevations in cholinergic signaling might produce maladaptive behaviors.[48] Stress induces increasing release of ACh in the PFC and hippocampus, whereas in amygdala stress has less effect on the release.[47,49] Stress also reduces firing of the cholinergic interneuron in the striatum.[50] Acute stress effects the changes in ACh signaling which leads to adaptive response for promotion of learning, changing behavior and avoiding stress.[50] However, chronic stress produces maladaptive behavior of ACh signaling leading to anxiety and mood disorders.[50] Hence, the PFC, hippocampus, and amygdala are important for modulation of cholinergic functions in stress reactions.

3.3.5 Gamma Aminobutyric Acid (GABA)

GABA is an inhibitory neurotransmitter in the brain because it reduces activity of the nervous system. The network of GABAergic interneurons in the amygdala is necessary for the brain's inhibitory circuit.[51] These neurotransmitters are important for keeping a balance between neuronal inhibition and excitation.[51] Prolonged stress exposure produces the changing in the limbic pathways and is susceptible to mood disorder, memory impairment, and epilepsy.[52,53] In the brain, GABA receptors play a central role in regulating both the short and long-term effects of stress. GABAergic neurons signaling in both acute and chronic stress models exhibit impairment in the hippocampal connections.[54,55] The inhibitory effects of GABA are regulated by potassium chloride co-transporter (KCC2) which provides neuronal chloride homeostasis. An imbalance of chloride ions causes neurological disorders, for instance epilepsy, autism, and schizophrenia.[56] Hewitt and co-workers reported that acute restraint stress results in down regulation of the KCC2, disruption of chloride gradients in CRH neurons, increment of GABA levels, and stimulation of the HPA axis which induces cortisol release.[57] Hence, the interruption of KCC2 transporter might affect GABA and create chloride imbalance leading to neurological and psychiatric illnesses.

3.4 The brain is remodeled after stress

Prolonged stress causes shrinkage of the hippocampal CA and the dentate gyrus (DG). The hippocampus has an important role in the production of dendrites and synapses of newly created or

existing neurons. Hippocampal neurogenesis consists of cell neuronal proliferation, differentiation, survival, and maturation of new neurons.[58] Stress-induced dendritic remodelling occurs partly via increasing the number of GRs, and is mediated by neurotropic factors including brain derived neurotropic factor (BDNF), corticotrophin-releasing factor (CRF), and endocannabinoids.[12] The activation of glucocorticoids receptors in hippocampus exerts negative feedback on the HPA axis activity, resulting in reducing of cortisol release at the end of the stress.[59] The actions of glucocorticoids involve both genomic and non-genomic pathways responsible for MRs and GRs in the brain. The activated glucocorticoid receptors modulate calcium buffering capacity in mitochondria.[60] Glucocorticoids regulate the endocannabinoid system, and enhance neurotransmission of glutamatergic, GABAergic, cholinergic, noradrenergic, and serotonergic neurons.[61] Either stress or glucocorticoid administration can stimulate the endocannabinoid signalling in the brain, and initiates the limbic-hypothalamic-pituitary-adrenal (LHPA) axis activation to modulate emotions and behaviors.

4. Effects of stress-induced cortisol secretion on memory process and mood

Stress triggers changes of neurobiological, neurochemical, and neurobehavioral responses of several brain regions.[62] Stress induces cortisol release, and has bidirectional effects on brain structures and functions. Chronic stress has negative effects on neural plasticity leading to memory deficit. On the other hand, prolonged stress impairs learning and memory by modulating corticosterone, neurotrophin, and the releases of various neurotransmitters.[62,63] Among the brain structures affected by chronic stress, the hippocampus is the most common brain area susceptible to chronic stress-induced impairments of neural plasticity.[64] However, Vogel and Schwabe reported that the effect of stress on memory depended on the duration of the stress and time point of the memory process (encoding, consolidation, and retrieval).[65] If the prolonged stress occurs before encoding, memory formation is impaired; however, if acute stress occurs before and after encoding, memory is improved.[65] Nevertheless, stress occurring before memory retrieval results in an inability to recall previously learned information.[65] The process of memory consolidation can be either enhanced or impaired by different manipulations administered near the time of encoding.[66] Cortisol has the capacity to modulate consolidation and retrival processess. The rising of cortisol levels during stress enhances memory consolidation.[66] By contrast, very low cortisol levels can impair the consolidation of both neutral and emotional information.[66] However, the impact of cortisol on memory retrieval is the opposite from that of the consolidation process. An elevation of cortisol levels can impair memory retrieval process.[67] When cortisol levels increase, the capacity to retrieve previously consolidated memory decreases.[67]

Cortisol has excitatory effects on the amygdala which is responsible for emotion. Cortisol stimulates amygdala activation when the level of norepinephrine (NE) is high.[68] Also, cortisol affects the control of emotional memory by amygdala and hippocampus.[68] In animal study, Roozendaal and co-workers reported that cortisol improved memory only in the presence of high NE in the amygdala.[69] In human study, Abercrombie and co-workers reported that cortisol enhanced memory during emotional arousal.[70] Joels and Krugers reported that effect of cortisol on neuronal functions including LTP depended on glucocorticoid dose, presence and timing of a stressor, and brain region studied.[71] Therefore, stress involve in either enhancing memory or inducing cognitive impairment depending on exposing duration of stress. Stress also affects memory processes and causes a change of cognitive performance. Table 1 shows stress-induced cortisol secretion and associated mood and memory.

5. The clinical benefits of measuring cortisol levels

It is well-recognized that cortisol is an essential steroid hormone that regulates various physiological processes of the body. Cortisol has a circadian rhythm controlled by circadian oscillator in the suprachiasmatic nucleus (SCN), which is situated in the hypothalamus. The cortisol levels are fluctuating during the day. At midnight, very low cortisol levels are observed; however, the cortisol levels are high in the early morning, and fluctuate throughout the day. Therefore, cortisol is regarded as a key mediator for regulation of daily diurnal pattern.[78] A normal cortisol level is important for maintaining health and well-being, but very high or low of cortisol level leads to significant morbidity. Cortisol levels are commonly used to determine the abnormality of the adrenal gland, pituitary gland, and hypothalamus. Hence, the cortisol levels are determined primarily for diagnosis

Table 1 Stress-induced cortisol secretion associated with mood and memory

CNS functions	Stress induction/ stress response	Subjects	Observations	Reference No.
Mood	Trier Social Stress Test/ salivary cortisol	Asthmatic patients with depressive mood	• Cortisol responses to acute stress depending on asthma and depressive mood. • Cortisol secretion was greater in asthmatics with depressive mood during acute stress.	72
	Psychosocial stress/ salivary cortisol	Schizotypal traits	• High schizotypal personalities reduce cortisol response after acute psychosocial stress. • High schizotypal personalities show delayed cortisol response compared with low schizotypal personalities.	73
	Noise and social stress/ saliva cortisol, subjective stress	Psychosis patients	• Psychosis patients reveal poorer emotion perception and more high-confident errors with increasing arousal. • Schizophrenia and healthy controls showed an increase of emotion perception errors with higher cortisol response.	74
Memory	Oral academic presentation (stressor condition)/ salivary cortisol	Male and female healthy condition	• Oral presentation caused higher cortisol levels than in the control condition. • Women have higher subjective stress than men. • Women had a lower cognitive appraisal compared to men.	75
	Trier Social Stress Test/ salivary cortisol	Healthy children	• Lower income children showed reduced hippocampal volume which related to poorer memory performance. • Hypo-reactivity in cortisol stress reactivity was associated with poorer memory among lower–income children.	76
	Socially evaluated cold pressor test (SECPT) and the control task/ salivary cortisol	Students	• The non-reward protocols, increasing stress-related cortisol in stressed subjects, were related to improved recognition. • The reward items, increasing stress-related cortisol, were not related to increases in memory performance.	77

and monitoring the treatment of patients. The interruption of the HPA axis activity mediates abnormal cortisol levels, which is implicated in human diseases, particularly Cushing's syndrome and Addison's disease.[4] Moreover, there are increasing risks of mood and cognitive disorders, found in patients with anxiety, depression, dementia, and cerebrovascular disease and so forth.[5-7] Nevertheless, the accuracy of diagnosis from a single cortisol measurement is limited by diurnal variation in cortisol concentration and the increment of cortisol levels during stress. Accordingly, more information for diagnosis can be derived by dynamic testing of the HPA axis.[79]

Cortisol is released from adrenal gland and then diffuses into the blood circulation. Cortisol is frequently transported in three forms: protein-bound cortisol, free cortisol, and cortisol metabolites. Therefore, clinical and research studies measure cortisol levels in various sample types such as blood, saliva, urine, and hair. The advantages and disadvantages of analysis in each sample types are as followings: (1) Blood sample, either serum or plasma, is a clinical standard method to evaluate cortisol levels. This is a direct measurement of total cortisol in both protein-bound cortisol and free cortisol. The sample is collected by venipuncture performed by medical technologist. Therefore, the test is the most invasive method because of the sample collection processes.[79,80] (2) Salivary sample is commonly used where serum or plasma is not applicable. This method reflects only free cortisol. Because saliva is easier to collect, the stress from venipuncture can be

avoided. The limitations of this sample collection, however, are from the contamination of saliva with any protein and filtering capabilities.[79-81] (3) For urine sample, this type of cortisol test is more comprehensive than the previous mentioned tests because the total amount of cortisol excreted into urine over 24 hours is determined. However, patients might have difficulties collecting urine sample over long period of time; it is also not suitable for patients with renal dysfunction.[79-81] (4) Scalp hair cortisol test is used to evaluate cortisol levels and the HPA axis activity over 3 months or more. Thus, this measurement is performed to determine chronic stress, but not suitable for acute stress. Cortisol derived from the scalp hair is a lipophilic substance from blood supply. Hair cortisol is from sweat and sebaceous glands. Hence, to determine cortisol from the hair, washing and extraction methods are needed.[81-82] There are numerous methods for measuring cortisol levels in the blood, saliva, urine, and hair. For example, radioimmunoassay (RIA), enzyme-linked immunoassay (EIA), chemiluminescent assays (CLIA) and liquid chromatography - tandem mass spectrometry (LC-MS) and so forth.[79] Table 2 summarizes the advantages, disadvantages, and limitations of cortisol measurement in several sample types.

6. Effect of cortisol on the risks of neuropsychological and neurodegenerative diseases

6.1 Effect of cortisol on the risks of depression

Depression is a serious mental disorder, and characterized by sadness and loss of interest. These conditions interrupt daily activities, and increase medical morbidity and mortality.[83] The World Health Organization (WHO) reported that depression was one of the most common mental disability worldwide.[84] The pathophysiology of depression is caused by dysregulation of the HPA system.[85] Continuously stressful lives are risk factors of depressive symptoms and the onset of major depression in both adolescent and adults.[86,87] About 40-60% of depressed patients have high plasma cortisol levels due to the stimulation of the HPA axis activity. The activation of the HPA system also causes interruption of the circadian

Table 2 Summary of the advantages, disadvantages and limitations of cortisol measurements in several sample types

Cortisol measurements (Sample types)	Advantages	Disadvantages	Limitations
1. Blood (serum/plasma)	• Standard and more specific measurements • Indicated as total cortisol, protein-bound cortisol, and free cortisol	• Venipuncture inducing stress • Subjects receive pain • Samples are collected by medical technologist	• Involves with diurnal rhythms functioning and are susceptible to confounding by environmental disturbance
2. Saliva	• Easy to collect samples • No stress on the subjects • Excellent specific measurement and high reproducibility	• Only free cortisol is detected • Contamination of saliva with any protein binding or filtering capabilities validate the measurement	• Repetitive determination is required because of the variation of diurnal rhythms.
3. Urine	• More comprehensive • Measure the total amount of cortisol excreted into urine for over a period of 24 hours	• Difficult to collect urine sample • Subjects get uncomfortable and not willing to do sample collection	• Not accurately reflects the cortisol levels in patients with moderate to high renal function impairments
4. Hair	• Not sensitive to changes in the circadian pattern of the HPA activity • Easy to collect samples • No stress on the subjects	• Not appropriate to acute stress • Only free cortisol is determined • The analysis is complex and involves many steps	• The impact of relative stressors that occurred during the period of hormone deposition is not detected • Suitable for researcher interested in psychosocial and environmental stressors

rhythm which regulates wake and sleep cycles.[88,89] Vreeburg and co-workers found that sixty minutes after awaking, patients with acute depression secreted more cortisol compared with control group.[90] Bhagwagar and co-workers also reported that depressed patients increased cortisol levels after awakening. They concluded that cortisol levels and depressive symptoms were associated with acute and chronic stress.[91] Pruessner and co-workers confirmed that depressed subjects had high cortisol levels in early morning when compared with non-depressed subjects.[92] Therefore, cortisol is one of a biomarker for depression. The patients with depression have high plasma cortisol caused by the interruption of the HPA axis activity. However, the correlation between stress-induced cortisol release and depressive symptoms is still controversial and under investigation by many research groups.

6.2 Effect of cortisol on the risks of anxiety

The prevalence of anxiety disorder has dramatically increased due to changes in society, economy, government, and environment. Anxiety disorder is an emotional state and characterized by increased alertness, fear, and physiological symptoms including increment of heart rate and blood pressure.[93] The alteration of the HPA system promotes high amounts of cortisol release which relates to anxiety disorder.[94] Moreover, the interruption of neuronal signaling between cortical and limbic system relates to negative moods such as anxiety and depression.[95]

There are numerous studies which describe the relationship between the activity of HPA axis and anxiety disorder. The research groups of Lenze and co-workers and Mantella and colleagues reported that elderly people with anxiety disorder had higher cortisol levels than those without disorder.[95,96] On the other hand, Hek and co-workers reported older adults with chronic anxiety had lower cortisol awakening response than those without. As a result, chronic anxeity led to down regulation of the HPA axis activity.[94] However, Heaney and co-workers reported no relationship between anxiety symptom scores and cortisol levels.[97] Hence, the relationship between cortisol levels and anxiety disorder is inconclusive. The variation might due to the differences in age of the participants, time of the cortisol collections, and the severity of anxiety disorder.

6.3 Effect of cortisol on the risks of Alzheimer's disease

Alzheimer's disease is characterized by irreversible and progressive brain deterioration which slowly destroys cognitive performance, thinking skill, and ability to solve problems. It is well-established that cortisol acts on the brain structures and associates in cognitive function.[98] The cognitive process is regulated by the activity of serotonin, ß-adrenergic receptor, calcium influx, and long-term potentiation (LTP).[98] The effects of cortisol on cognition are complex and involve various cognitive domains and several brain regions. The differences in cortisol levels are likely to affect either positive or negative effects in cognitive domains.[7, 98] Some of these effects are acute; however, some are chronic effects on structures and functions of the brain.[98] The modification of the HPA axis activity with raised cortisol levels in elderly people is related to an increased risk of Alzheimer's disease.[7] The brain volumes of Alzheimer's patients with high cortisol levels are decreased leading to cognitive dysfunctions.[7, 98] The clinical studies found the correlation between cortisol levels and cognitive performance among non-demented elderly adults.[98,99] The studies reported that high cortisol levels led to poor cognitive performance.[98,99] Moreover, some studies determined the relationship between cortisol levels and episodic memory; the studies reported that the elevation of cortisol levels impaired episodic memory among older adults without dementia.[100,101] Several studies determined the correlation between cortisol levels and prefrontal cortex which mediated cognitive functions including speed of memory, executive function, and working memory.[102-104] These studies showed poor cognitive performance in all domains for people with high cortisol levels.[102-104] Hence, elderly people with high cortisol levels have high risk for cognitive impairment.

6.4 Effect of cortisol on the risks of cardiovascular diseases

Cortisol has direct effects on hearts and blood vessels, expressed on both MRs and GRs, and modified by the activity of 11ß-hydroxysteroid dehydrogenase enzymes.[105] Cortisol binds with GRs on vascular smooth muscle leading to increasing vascular contractility, but reducing vascular migration and proliferation. However, binding of cortisol with MRs on vascular smooth muscle induces perivascular inflammation and vasoconstriction.[105] In the

endothelial cell, bindings of cortisol with GRs and MRs result in different vascular effects; binding of cortisol with GRs reduces endothelium-dependent vasodilation and angiogenesis, whereas binding of cortisol with MRs shows either enhancing and diminishing vasodilation effects.[105] Thus, cortisol is a key hormone for maintaining normal blood pressure; however, an excess of cortisol could cause hypertension.[106] The dysregulation of the HPA axis promotes vascular inflammation, rising blood pressure due to vasoconstriction, renal sodium retention, and vascular volume expansion which might increase risks of cardiovascular diseases.

7. Pharmacologic uses of glucocorticoids

Natural and synthetic glucocorticoid drugs are commonly used in both endocrine and non-endocrine disorders.[107] In endocrine dysfunction, glucocorticoids are given for diagnosis of Cushing's syndrome and for the treatment of patients with Addison's disease and congenital adrenal hyperplasia.[107] In contrast, non-endocrine disorders, glucocorticoids are recommended for inflammatory, allergic, and immunologic diseases.[107] The common names of glucocorticoids drugs are hydrocortisone, cortisone, prednisolones, prednisone, methylprednisolone, triamcinolone, and dexamethasone.[108,109] The side effect of these drugs is suppression of the HPA function leading to the low production of CRH and ACTH. As a result, adrenal gland is malfunction and unable to secrete cortisol.[108,109] The glucocorticoids administration depends upon the dose, timing, and duration of treatment for given patients.[109] Depending on the diagnosis and severity of the diseases, patients should consult with their physicians to avoid adverse effects such as osteoporosis, skin thinning, weight gain, mood disorders, and memory impairment.[110] Other factors that might contribute to such adverse effects include repetitive doses and prolonged duration of treatment.[111] Therefore, physicians should use the lowest dose of glucocorticoids for the short period, and carefully monitor patients under the treatment for reducing the adverse effects.

8. Effects of stress on health and strategies to reduce stress, improve mood and memory

Chronic stress has been implicated as the cause of abnormalities of stress hormones and inflammatory markers. These hormonal and immune dysfunctions are related to health problems such as metabolic syndrome and cardiovascular disease.[112] High levels of cortisol are associated with metabolic disturbances including raised blood glucose and elevated systolic blood pressure.[113] Additionally, increasing circulating pro-inflammatory cytokines (interleukin-6 (IL-6)) produces metabolic syndrome elements comprising of high Body Mass Index (BMI), diabetes type 2, and coronary artery disease.[114] Thus, stress is a critical health problem leading to high risks for diseases. Therefore, the strategies to reduce stress are important for improving health. There are several ways to reduce stress as follows:

(1) Meditation is a mind and body training. Meditation is a method used for teaching practitioners to observe feelings, senses, and thoughts in a non-judgmental manner. Mindfulness meditation helps participants to pay attention to events with openness and acceptance. Thus, meditation may encourage practitioners to approach rather than avoid sad thoughts and feelings, which may reduce cognitive distortions and avoidance.[115] Poulin and colleagues reported that mindfulness training for 30-minute every day for four weeks could reduce stress and promote well-being of participants.[116] Amutio and co-workers demonstrated that people who performed mindfulness training for 2.5-hour per month for 10 months had enhanced positive mood and relaxation state.[117]

(2) Yoga is a technique increasingly used for reducing stress. The mind-body interventions including yoga, mindfulness meditation, tai chi, and qi gong affect mental and cognitive functions related to aging.[118-120] Eyre and co-workers reported that subjects with mild cognitive impairment who participated in yoga showed improved verbal memory performance associated with increased neural connectivity between default mode networks in the frontal cortex, cingulate cortex, and occipital cortex.[121] Maddux and co-workers reported that participants with moderate to high stress who performed yoga for one hour everyday for 16 weeks had reduced stress and anxiety.[122]

(3) Aerobic exercise is a physical fitness at low to moderate intensity exercise for improving cardiovascular activity. Examples of aerobic exercises are running, walking, boxing, swimming, and dancing. After physical exercise at high intensity for 30 minutes, subjects raised saliva cortisol and serum BDNF. Better retention of vocabulary was demonstrated comparing

with a relaxed control group.[123] Exercise enhanced an expression of BDNF and neurogenesis of dendritic spine in the perirhinal cortex and hippocampus which correlated with better learning and memory.[124,125]

(4) Avoiding high fat-high salt diets: High fat and salt diet is malnutrition and results in high risk of cognitive dysfunction and cardiovascular disease. High-salt diet-treated mice demonstrated impaired short-term and long-term memory in novel object recognition task and fear conditioning tests.[126] Increasing of reactive oxygen species (ROS), and down regulation of expression of synapsin I, synaptophysin, and BDNF in the hippocampus can cause memory impairment.[126] Consumption of high fat diet impaired spatial memory in rats and increased body weight, blood pressure, and triglyceride levels. Rats fed with high fat and high cholesterol diets showed increased microglia activation and altered BBB, contributing to spatial memory deficit.[127,128] The high-fat diet in the mices resulted in obesity, significant impairment in glucoregulation, and modified insulin-mediated signaling within the hippocampus.[129] Furthermore, consumption of high salt and high fat diets led to an increased risk of dementia related to Alzheimer's disease.[130] Therefore, high fat-high salt diets contributed to increasing risk of Alzheimer's disease, metabolic syndrome, and cerebrovascular disease. Thus, one should avoid diets containing high fat and high salt for reducing the risk of these diseases.

Conclusion

Stress is the emotional strain resulting from problems in life. Stress-induced cortisol secretion is controlled by the HPA system. Cortisol affects several organs which regulates physiological functions of various body systems. In the CNS, cortisol passes through the BBB and modulates neurotransmitter activity in the cortical and subcortical brain regions. The brain contains MRs and GRs that produce positive or negative effects on mood and memory depending on blood cortisol levels. The abnormality of cortisol levels could enhance risks of the psychological and neurodegenerative diseases associated with mood and cognitive disorders. However, there are numerous ways to reduce stress and enhance mood and memory, for instance, meditation, exercise, and consuming healthy foods. Glucocorticoids drugs are used for treatment of endocrine, inflammatory, allergic, and immunologic disorders. Patients should consult with their physicians before taking the drugs to avoid adverse effects.

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Conflict of interest

None to declare.

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