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The Neuroscientific Basis of Stress-related Psychiatric Diseases

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Abstract

This article summarizes brain symptoms, related diseases, social adjustment, and features of behavior that are associated with chronic fatigue and insomnia and may be important for disease prevention, based on recent findings on stress and brain function and morphology. These results, modulation of mental function occurs, it is known that to develop mood disorders or schizophrenia, stress and anxiety disorders. Our research results presented here, it is part of the dissemination projects related to 13 the field of disease research and development and work-related accidents and Japan Labor Health and Welfare Organization.

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—Key words—

hypothalamic-pituitary-adrenal axis (HPA axis), hypofrontality, neuroethics

1. Introduction

Endocrine function of the hypothalamic-pituitary-adrenal axis (HPA axis) plays a pivotal role as the mechanism against stress in the brain. With prolonged stress, excess corticotropin releasing factor (CRF) is released in the HPA axis and cortisol increases in the body. This may affect cerebral neural plasticity, weaken the mechanism against stress, and lower the threshold for onset of psychiatric disorders such as depression. Continuous elevation of serum cortisol inhibits neurogenesis in CA1, CA3 and the granule cell layer of the hippocampus. This affects the HPA axis, and persistent hyperactivity of the HPA axis may affect the emotional state.

Morphological analyses have shown a significant decrease in hippocampal volume in patients with depression or posttraumatic stress disorder (PTSD), and have indicated that stress strongly affects brain-derived neurotrophic factor (BDNF), which plays a significant role in neurogenesis and neurodevelopment. BDNF in blood decreases in patients with depression and there is a significant negative correlation between the levels in blood and the severity of depression[1]. BDNF in blood is also lower in healthy individuals with greater stress[2].

Excessive release of CRF also influences γ-aminobutyric acid (GABA), a monoamine inhibitory neurotransmitter in the brain, and inhibits the serotonin nervous system extending from the dorsal raphe nucleus to the prefrontal cortex (PFC), which is associated with hypofrontality in patients with depression. CRF itself also has an arousal effect, and thus HPA axis hyperactivity may be induced by sleep deficit and may be associated with depression[3].

These biological findings in psychological and social studies of stress reinforce the theory concerning the mechanism relating chronic insomnia and stress to fatigue and onset of depression. We have shown negative correlations between severe overwork and cortisol levels and the cortisol/DHEA ratio in females[4]. Therefore, it is clear that an appropriate work environment is important from the perspective of mental health in industry.

2. Fatigue and Depression

Metabolism of serotonin (5-HT) is decreased in the frontal lobe of patients with depression, and PET/

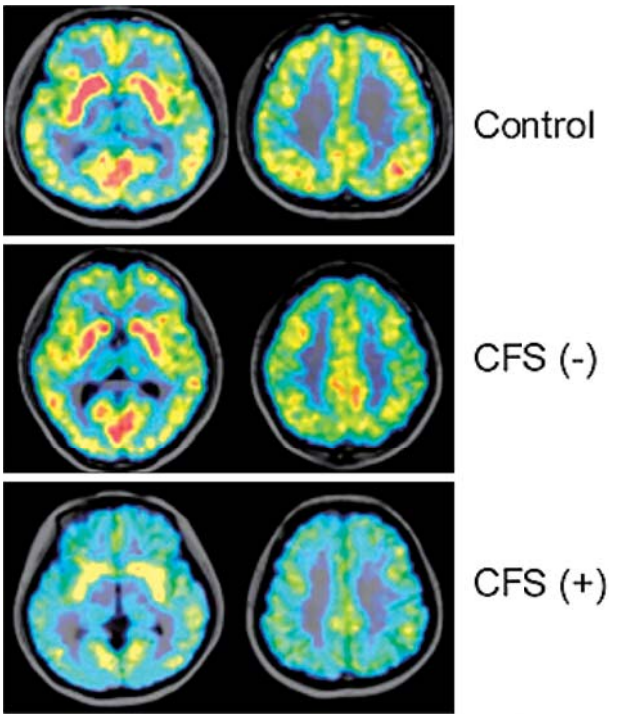

Fig. 1 Differences in mAChR expression on PET images in patients with chronic fatigue syndrome (CFS) with or without mAChR autoantibody[9]. mAChR expression in CFS patients without mAChR autoantibody (middle panel) was similar to that in healthy individuals (upper panel), whereas mAChR expression decreased in CFS patients with mAChR autoantibody (lower panel).

SPECT images indicate that hypofrontality is correlated with decreased blood flow in the PFC and decreased glucose metabolism, which reflect depression. Drevets[5] proposed that mood state, such as depression, may be associated with decreased cerebral blood flow (CBF) and glucose metabolism in the subgenual and dorsal PFC, increased CBF and glucose metabolism in the ventral PFC, and structural abnormality in all of these regions. Our previous studies using ^{99m}Tc-ECD SPECT confirmed hypoperfusion of the anterior cingulate gyrus (anterior cingulate cortex (ACC)), left PFC hypoperfusion and decreased blood flow in the dorsal part of the frontal lobe, which was correlated with subjective fatigue and sleep deficit[6].

Management of insomnia and fatigue is an important measure against stress in the field of industrial health and preventive medicine, since these conditions may cause psychological fatigue associated with hypofrontality during the depressive phase[7]. Measurement of brain function using fMRI during neuropsychological tasks also indicates that hypofrontality is correlated with psychomotor inhibition and poor concentration[8]. PET analysis in patients with chronic fatigue syndrome (CFS) showed that severe fatigue and malaise are correlated with ACC hypoactivity[9]. A recent study suggested that neurotransmission is decreased in CFS patients with autoantibodies to muscarinic acetylcholine receptor (mAChR)[10] (Fig. 1). These findings explain chronic psychological fatigue caused by prolonged insomnia, overtime, and stress, as a sign of motor and cognitive dysfunction resulting from decreased metabolism and blood flow in the PFC and ACC[11].

3. Psychiatric Diseases

(1) Depression

The monoamine hypothesis suggests that depression is caused by a lack of monoamines (noradrenaline (NA), serotonin (5-HT), dopamine (DA)), which are closely associated with emotion. However, there is no evidence showing a lack of monoamine metabolites during the depressive phase or an increase in monoamine levels in the brain at a few hours after treatment with antidepressants, although this effect may be delayed. Other neurotransmitters, G proteins, the cAMP-responsive element binding protein (CREB) transcription factor, and BDNF may also have roles in depression. Clinical studies, including those using PET/SPECT at rest and fMRI for measurement of activation during performance of tasks, have shown hypofrontality in the ACC, dorsolateral PFC, and subgenual cortex (Fig. 2). Noninvasive and convenient-to-handle near-infrared spectroscopy (NIRS) has been approved by the Ministry of Health, Labour and Welfare in Japan in April 2009 as medical technology for differential diagnosis of depression using optical topography[12]. As mentioned above, the hippocampal volume is decreases by HPA axis hyperactivity during the depressive phase, but is inversely proportional to the frequency of the phases and disease duration. Thus, the number of studies on BDNF, which is closely related to neurogenesis, has increased, and improved understanding of methylation of the BDNF gene may promote more objective diagnosis of depression[13].

(2) Schizophrenia

Abnormal dopamine function is the most common pathology of schizophrenia. Thus, correlations between dopamine D_2 receptor inhibition and drug dosage have been examined, along with PET analyses of dopamine

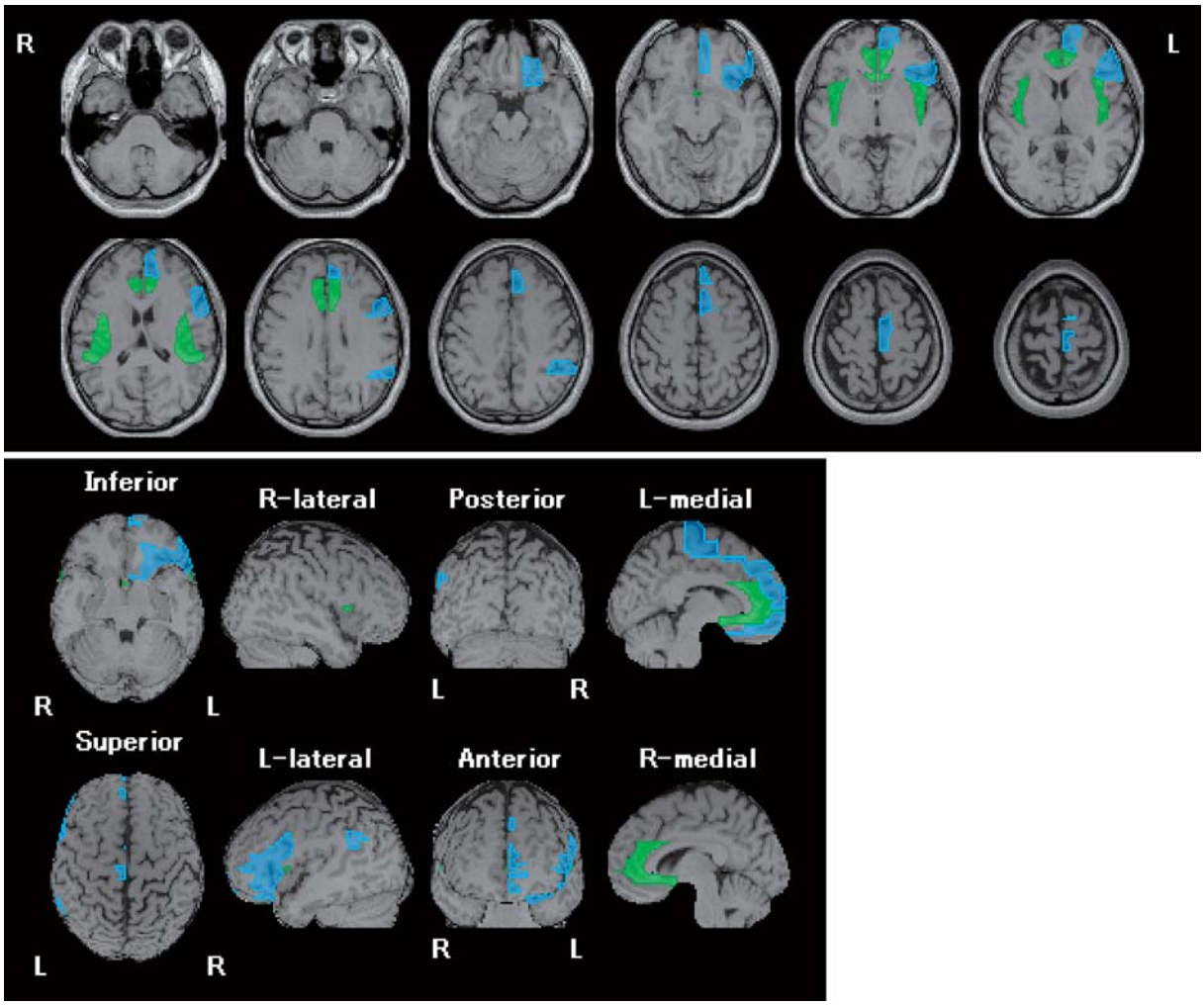

Fig. 2 Regions with decreased CBF in patients with depression. The greatest decrease in CBF occurred in the ACC, based on voxel based stereotactic extraction estimation (vbSEE) analysis. Upper panel: horizontal section; lower panel: brain surface. (Koyama et al. 2010)

neurotransmission in the brain. PET/SPECT at rest shows that blood flow and metabolism in the temporal lobe and basal ganglion increase, in addition to relative hypofrontality, which might be related to the symptoms and treatment of auditory hallucination[14]. Regarding morphology, the volume of the left superior temporal gyrus and medial temporal lobe are reduced. A study on at risk mental state (ARMS)[15] found partial and gradual volume reduction in the left superior temporal gyrus. Negative symptoms and cognitive impairment have also been associated with PFC abnormalities, and may explain working memory disorders.

(3) Panic disorder

Previous studies on neurotransmission in anxiety and fear have suggested that the amygdala is an important site in panic disorder (PD). Hyperactivity in this site might cause abnormal excitation in the hypothalamus, locus ceruleus, periaqueductal gray matter, and other regions, and induce symptoms such as panic attack, avoidance response and sensory defensiveness. There are abundant serotonergic terminals in the lateral and basal nucleus of the amygdala. The serotonergic terminals enable selective serotonin reuptake inhibitors (SSRIs) to act on these regions and have an effect on PD. Hyperactivity of the amygdala, hippocampus, and brainstem causes panic attack, which suggests that this might be associated with hypoactivity in the orbitofrontal area, ACC, and dorsomedial PFC. Regarding morphology, Asami et al.[16] showed that the volumes of the right amygdala, PFC, and insular cortex were significantly decreased in patients with PD, using MRI and voxel-based morphometry.

(4) Posttraumatic stress disorder

A traumatic event occurs as an environmental factor in the pathology of PTSD, in contrast to other functional psychiatric disorders. Therefore, an understanding of PTSD may be a key in determining changes in the body caused by exposure to stress. Decreased hippocampal volume in patients with PTSD was first reported in 1995. Gilbertson et al.[17] subsequently found that the hippocampal volume was significantly smaller in both combat-related trauma-exposed patients and in non-trauma-exposed identical twins of these patients, compared with non-PTSD controls. In addition, in patients with PTSD after the sarin gas attack on the Tokyo subway system in 1995, the symptoms were more severe in those with a lower volume of the left ACC. These findings suggest that some dysfunction of the ACC in patients with PTSD might cause repeated flashbacks of the trauma experience and fearful stimuli that can usually be avoided in daily life, but cannot be completely removed from memory. The pathology may also involve genetic factors, based on studies including that of Gilbertson et al. above. However, Kasai et al.[18] only found a lower ACC volume in combat-related trauma-exposed patients with genetic vulnerability to PTSD, which suggests a possible correlation between environmental (presence or absence of a traumatic experience) and genetic factors.

4. Prospect

As described above, prolonged exposure to stress activates CRF nerves, inhibits the serotonin nervous system from the dorsal raphe nucleus, and damages ventrolateral PFC function. Arita et al.[19] proposed an association of socially deviant behavior such as loss of temper and suicidal impulse with the PFC, based on lost control of impulsivity and violence due to damage to the ventrolateral PFC. In general, serotonin release decreases in patients with depression, and such a decrease in the ventrolateral PFC may particularly lead to uncontrollable depressive and impulsive actions and may be linked to suicide.

fMRI studies of brain function while lying (lying and truth-telling, go/no-go tasks) indicate activation of the ventrolateral and medial PFC, and activation of the ventrolateral PFC may inhibit impulsivity (no honesty (go response), but other actions (no-go response) and guilt). In a fMRI study on changes in brain function in healthy volunteers, Takahashi et al.[20] found that the medial PFC and posterior superior temporal sulcus were activated during feelings of guilt and embarrassment. Thus, these brain regions may be related to the ability to understand the intention of others and to self-examination[21]. These findings suggest that neuroscience can reflect general morals, guilt and embarrassment, and encourage appropriate thought and self-examination for promotion of social adjustment.

Advances in neuroscience have clarified brain functions that are related to impulsivity and suicidal intent, and permit screening for development of diseases and life-threatening conditions. However, if brain regions linked to emotion can be identified systematically, individual social adjustment and behavior can be appropriately classified and modifications based on this classification may be possible. These features of brain function may be very useful for providing appropriate approaches for disease prevention and strengthening resilience against stress. This also indicates the need for a greater focus on neuroethics, in order to protect people from inappropriate use of this science for manipulation of intentions and beliefs.

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ストレス関連精神疾患と脳科学知見

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—キーワード—
視床下部—下垂体—副腎皮質系，前頭葉機能低下，脳神経倫理

本稿では，ストレスと脳機能・形態に関する最近の国内外の研究知見から，蓄積疲労や不眠など疾病予防上重要な症候や状態像およびストレス関連精神疾患における脳科学的知見を中心に述べる．特に，労働衛生上問題となる過重労働等にともなう蓄積疲労や慢性の睡眠不足および心理社会的ストレスは，脳内ストレス適応機構に影響し，神経伝達物質や視床下部—下垂体—副腎系（HPA 系）の機能変化を介して精神変調を惹起し，気分障害や統合失調症，ストレス障害，不安障害等の発症閾値を低下させることが知られている．これらの生物学的知見を産業現場などの心理・社会的領域に展開すれば，不眠・ストレス・過労から疲労蓄積を伴い，場合によってはうつ病化に至るといった，ストレス曝露から経時的に疾病性が生じる論理が強化される．これまで脳形態学的には，うつ病や PTSD 患者における海馬容積の低下を認める報告が多く，これには神経細胞新生や神経発達に重要な脳由来神経栄養因子（brain-derived neurotrophic factor：BDNF）がストレスの影響を受けることが強く関連しているなど，従来の内分泌や神経伝達物質，脳内モノアミン類以外にも病態解明につながる新知見が蓄積されている．また，脳機能的検討では，強い疲労と前帯状回との関連や，うつという状態依存性にみられる前頭葉機能低下が示されてきたが，さらには社会適応性（衝動性とその自制など）と前頭前野との関連についても研究が進み，性格傾向や行動パターンと関連した脳機能的検討も多く行われている．その成果として，疾病予防やストレス耐性の強化等につながる対策が打ち出されることは当然有用であるが，仮に偏向的な応用により性格や行動特性の分類が容易になされ，人の個性や自由意思，アイデンティティなどへの侵害が起こらないために，neuro-ethics（脳神経倫理）が今後一層重視されるべきであろう．

利益相反：利益相反基準に該当無し

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