ABSTRACT  Depression is one of the five leading causes of disability and disease burden worldwide. Neurotransmitters and hormones have been the focus of pathogenic studies in depression. Since knowledge of depression’s neurophysiology has become more advanced, evidence currently shows that in depression underactivation of serotonergic and noradrenergic systems play major roles in the pathogenesis of neurotransmitters, while elevated hypothalamic-pituitary-adrenal (HPA) axis activity is a hallmark of stress responses and hormonal dysfunction. Other hormones such as thyroid hormones, growth hormone, prolactin and gonadal hormones have also been found significant. Recently, there has been greater concern that Brain-derived neurotrophic factor (BDNF) might also be involved in the pathogenesis of depression. Future research may shift from dealing with neurotransmitters to focus on the interventions that modulate the HPA axis and BDNF for the treatment of depression. Chiang Mai Medical Journal 2009;48(1):35-41.

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important neurobiological systems involved in the pathogenesis of depression, as well as the role of Brain-derived neurotrophic factor, which has recently been of interest.

**Neurotransmitters in depression**

The main focus of neurotransmitter research has been driven by the ‘monoamine hypothesis’ of depression,\(^2\) which states that a deficit of monoamine neurotransmitters; mainly serotonin, norepinephrine and dopamine, underlies depression.

**Serotonin**

Several studies have demonstrated that serotonergic dysfunction plays the major role in the pathogenesis of depression. Tryptophan, a precursor of serotonin, was found to be low in depressed patients\(^3\) and tryptophan depletion has been known to cause relapse in patients with a history of depression.\(^4\) Genetic variants of tryptophan hydroxylase, a rate-limiting enzyme in the synthesis of serotonin, were also found to be associated with suicidal behavior.\(^5\) Furthermore, previous studies focusing on serotonin metabolism have suggested that metabolism decreased in depressed patients when a low level of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, was found in the cerebrospinal fluid.\(^6\)

Serotonin receptors have also been found to relate to depression. Positron emission tomography (PET) has demonstrated the reduction of 5-HT1A receptor binding in patients with major depression, both presynaptically in the raphe nuclei and postsynaptically in several cortical regions.\(^7\) Moreover, some researches have shown that long-term antidepressant treatment leads to the downregulation of the 5-HT2A receptor\(^8\) and upregulation of the 5-HT1A receptor.\(^9\)

In terms of the serotonin transporter (5-HTT), single photon emission computed tomography (SPECT) studies found reduced serotonin transporter binding sites in depressed patients.\(^10\) This decreased reuptake of serotonin is believed to be a compensatory mechanism to counteract transmission deficits in some serotonergic systems. In addition, gene-environment interaction studies have suggested that subjects exposed to environmental stress are more likely to develop depression if they have at least one allele of a ‘low-efficiency’ version of the serotonin transporter.\(^11\)

**Norepinephrine**

Norepinephrine is also believed to play a major role in the pathophysiology of depression. Previous research has demonstrated a correlation between the downregulation of postsynaptic B-adrenergic receptors and clinical antidepressant responses, as well as the clinical effectiveness of antidepressants with noradrenergic effects (e.g. desipramine, venlafaxine, duloxetine).\(^12\) Moreover, an increased density of \(\alpha_2\)-adrenergic receptors has also been reported in depressed patients and suicide victims.\(^13\) This upregulation may be due to a relative deficiency of norepinephrine in the synaptic clefts. Finally, the reduction of urinary excretion of the metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) was found in patients with depression,\(^14\) although some subgroups of patients manifested elevated circulating levels of norepinephrine and its metabolites.\(^15\)

**Dopamine**

Previous studies have suggested that dopamine activity may be reduced in depres-
Pathogenesis of depression

Medications and diseases that reduce dopamine concentrations (e.g. reserpine, parkinsonism) were found to be associated with depressive symptoms. In contrast, drugs that increase dopamine concentrations (e.g. tyrosine, amphetamine, bupropion) have shown antidepressant efficacy.\(^{(16,17)}\)

**Acetylcholine**

An abnormal level of choline, a precursor to acetylcholine, was found in the brain autopsies of some depressed patients. Additionally, a cholinergic agonist can produce lethargy and psychomotor retardation, which mimic depressive symptoms as well as exacerbate symptoms in depressed patients.\(^{(18)}\)

**Gamma - aminobutyric acid (GABA)**

Reduced GABA levels in plasma and cerebrospinal fluid have been observed in depression. Animal studies have found that chronic stress can diminish GABA levels and some antidepressants were found to upregulate the GABA receptors.\(^{(19)}\)

**Glutamate and Glycine**

Glutamate and glycine, the major excitatory and inhibitory neurotransmitters in the brain, bind to N-methyl-D-aspartate (NMDA) receptors. An excess of glutamatergic stimulation can cause neurotoxic effects and research evidence has suggested that NMDA receptor antagonists have antidepressant effects.\(^{(20)}\)

**Hormones in depression**

**Hypothalamic-pituitary-adrenal axis**

The hypothalamic-pituitary-adrenal axis (HPA axis) is a complex set of direct influences and feedback interactions between the hypothalamus, pituitary gland and adrenal glands. Stress is perceived by the cortex of the brain and transmitted to the hypothalamus, where corticotropin-releasing hormone (CRH) is released onto pituitary receptors. Adrenocorticotropic hormone (ACTH) is then secreted from the anterior pituitary in response to CRH and results in the secretion of corticotropin into the plasma, stimulation of corticotropin receptors in the adrenal cortex and release of cortisol into the blood.\(^{(21)}\)

Elevated HPA activity is a hallmark of stress responses and depression.\(^{(22)}\) Increased 24-hour urinary free cortisol, serum cortisol and cerebrospinal fluid concentrations of cortisol were found in depressed patients.\(^{(23)}\) Previous research has suggested that the hypercortisolism in depression is possibly due to decreased inhibition of feedback from the hippocampus. The dexamethasone suppression test (DST) showed nonsuppression of cortisol secretion subsequent to the administration of synthetic glucocorticoid dexamethasone in about half of the most severely depressed patients, while antidepressant-induced clinical remission is accompanied by reversal of some of these abnormalities.\(^{(24)}\)

The dexamethasone/corticotropin-releasing factor (DEX/CRF) test demonstrated enhanced ACTH and cortisol in response to CRH when compared with control subjects.\(^{(25)}\) Since repeated studies in depressed patients and suicide victims have found elevated concentrations of CRF in cerebrospinal fluid when compared to patients with other psychiatric disorders and healthy controls,\(^{(26)}\) this blunted ACTH response to CRH challenge may be caused by the downregulation of pituitary CRH receptors.

Corticosteroid receptors, especially the glucocorticoid receptor (GR), are also believed to play an important role in the reg-
ulation of HPA axis. Evidence of impaired HPA negative feedback in depressed patients suggests the possibility that the number or function of GR is decreased.\(^{27}\)

HPA axis activation has been found to associate with structural changes in components of the axis. Neuroimaging studies have found an increased volume of both pituitary and adrenal glands in patients with depression,\(^{28,29}\) although this might be a state rather than a trait marker of depression, as a significant decrease in volume after successful treatment was reported.\(^{30}\)

Finally, it was found that healthy non-depressed subjects with high familial risk or depression exhibit disturbed HPA axis activity, as induced by the DEX/CRF test, suggesting that dysfunction of the HPA axis in depressed patients might be genetically transmitted.\(^{31}\)

**Thyroid Hormone**

A subgroup (5-10\%) of depressive patients had undetected thyroid dysfunction as reflected by an elevated basal thyroid stimulating hormone (TSH) level or an increased TSH response to a thyroid releasing hormone (TRH). Moreover, a blunted TSH response to TRH challenge was found to associate with relapse despite preventive antidepressant therapy.\(^{32}\)

**Growth Hormone**

Growth hormone is secreted from the anterior pituitary after stimulation by noradrenaline and dopamine. Secretion is inhibited by somatostatin and CRH. Decreased cerebrospinal fluid somatostatin levels have been reported in depression.\(^{33}\)

**Prolactin**

Low prolactin level and decreased prolactin response to the D-fenfluramine challenge test were found in depressed patients.\(^{34}\) This might be associated with postpartum depression, as the level of prolactin is lower at the time of delivery.

**Gonadal hormones**

Depressed premenopausal women have a higher intensity of menopausal symptoms, a significantly lower concentration of estradiol, and a higher level of follicular stimulating hormone (FSH) than non-depressed women.\(^{34}\)

**Brain-derived neurotrophic factor in depression**

Brain-derived neurotrophic factor (BDNF) is a neurotrophic peptide believed to support the growth, differentiation and survival of neurons. Recently, there has been greater concern that BDNF might be involved in the pathogenesis of depression, as the monoamine hypothesis could not explain the delay between increasing monoamines and clinical improvement of depression. Clinical studies have found that successful treatment, with a dual serotonin-noradrenaline reuptake inhibitor, results in increased serum BDNF levels.\(^{35,36}\) Moreover, the level of BDNF was found to be downregulated by stress and cortisol,\(^{37}\) and upregulated by antidepressants.\(^{38}\) A postmortem study in depressed patients who committed suicide also found a reduction of BDNF in the hippocampus.\(^{39}\)

**Conclusion**

The pathogenesis of depression is complicated and involves multiple biological systems as well as psychosocial factors. The involvement of neurotransmitters, hormones and BDNF in the pathogenesis of depression is of particular interest, but not yet fully
understood. However, stress seems to be an important factor in disturbing both systems. Future research may shift from dealing with neurotransmitters to focusing on the interventions that modulate the HPA axis and BDNF for the treatment of depression.

References


บทบาทของสารสื่อประสาท ฮอร์โมน และ BRAIN-DERIVED NEUROTROPHIC FACTORS ในการเกิดโรคซึมเศร้า

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บทคัดย่อ โรคซึมเศร้าเป็นโรคที่พบได้บ่อยและถือว่าเป็นหนึ่งในหัวหนึ่งของโรคที่เป็นภาระโลก สาเหตุทางชีววิทยาหลักของโรคซึมเศร้าที่ได้รับความสนใจ ได้แก่ การเปลี่ยนแปลงของสารสื่อประสาทและฮอร์โมน งานวิจัยทางสารสื่อประสาทพบการทำงานลดลงของระบบซีโรโตนินและนอร์อะดรีเนอร์คัมในขณะที่งานวิจัยด้านฮอร์โมนพบการทำงานที่มากเกินไปของระบบ hypothalamic-pituitary-adrenal (HPA) axis จากการตอบสนองต่อความเครียดเป็นสาเหตุหลักของโรคซึมเศร้า ฮอร์โมนอื่น ๆ ที่พบว่าเกี่ยวข้องกับโรคซึมเศร้าได้แก่ ฮอร์โมนไทรอยด์ โปรแลคติน โปรแลคติน โปรแลคติน และฮอร์โมนเพศ นอกจากนี้โรคซึมเศร้านั้นถูกวิจัยพบว่า brain-derived neurotrophic factor (BDNF) ซึ่งเป็นสารที่ช่วยการเจริญเติบโตของเซลล์ประสาทสัมพันธ์กับการเกิดโรคซึมเศร้า ด้วย การวิจัยถือว่าการวิจัยด้านโรคซึมเศร้าอาจเปลี่ยนทิศทางจากการวิจัยเกี่ยวกับยาที่ปรับสารสื่อประสาทไปยังการวิจัยที่จัดการกับ HPA axis และ BDNF ต่อไปในอนาคต เขียนโดย

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คำสำคัญ: ซึมเศร้า, สารสื่อประสาท, ฮอร์โมน, brain-derived neurotrophic factor