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Review Article

A REVIEW: HYPOTHESIS OF DEPRESSION AND ROLE OF ANTIDEPRESSANT DRUGS.

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ABSTRACT

There is very vast empirical work that directly assesses the neurobiological association of neurochemicals and biochemical super factors with the liability to depression. Therefore, as a means of providing a framework for future research, this article outline the path physiology arises as a consequence of altered regulation of particular brain chemicals. In addition, cell and molecular biology have proved useful to study the mechanisms of information processing, plasticity and neuronal survival involved in depression. The literature derived from popular neurophysiologic theories of depression, biobehavioral research, and human work is discussed where available. In an attempt to explore the association of this framework to depression the present article reviews the evidence from both clinical and experimental studies which implicates hypothesis of depression and the mechanism from which antidepressant drug act for the maintenance of depressive illness. Present studies evolving hypothesis of the pathosphysiology, catecholamine, Sleep alterations, Glucocorticoids, the Neurotrophic, HPA axis overdrive, Hypothyroidism, Emotionality and altered activity in depression and treatment of depression involves adaptation or plasticity of neural systems. This hypothesis was based on a correlation of the psychological and cellular actions of a variety of psychotropic agents. This will be used as experimental tools to study pharmacological action of antidepressant drug.

Keywords: Information processing, Plasticity, Neuronal survival, Depression, Antidepressant.

INTRODUCTION

In reviewing the literature on the physical aspects of depression one is hampered by the lack of any uniform concepts to structure of various phenomenan. Psychologists can only investigate the physical manifestations that we can observe in the form of behavior. Knowledge of the function of brain regions under normal conditions suggests the aspects of depression to which they may contribute. But no one knows the precise mechanism that triggers clinical depression. Because of the vast number of central neurobiological variables that are relevant to behavior, a theoretical strategy is needed to guide selection of the neurobiological variables hypothesized to relate.

In the early 20th century the explanation of mental illness changed from a disease of the 'mind' to a proper brain dysfunction. It is widely accepted that a neurochemical imbalance underlies the pathophysiology of mood disorders. Neurochemical imbalances, namely in the synthesis and secretion of norepinephrine and serotonin, are thought to underlie depression. This view is supported by clinical evidence that pharmacotherapies that enhance noradrenergic and/or serotonergic transmission effectively relieve symptomatology, albeit with some delay. Since a whole spectrum of behaviors is disrupted during depressive episodes, it is unlikely that dysregulation of a single neuroanatomical substrate can account for the disorder. Networking between different anatomical and neurochemical substrates in the onset of and recovery from depression[1].

However, recent studies demonstrate that structural alterations may also occur in response to stress and in patients with mood disorders. Neuronal plasticity is a fundamental process by which the brain acquires information and makes the appropriate adaptive responses in future-related settings. Dysfunction of these fundamental processes could thereby contribute to the pathophysiology of mood disorders, and recovery could occur by induction of the appropriate plasticity or remodeling [2]. Moreover, reviews of literature demonstrate that these structural alterations are reversible upon administration of antidepressants.

Catecholamine hypothesis

In the 1960s, the "catecholamine hypothesis" was a popular explanation for why people developed depression. This hypothesis suggested that a deficiency of the neurotransmitter or norepinephrine (also known as nor adrenaline in certain areas of the brain was responsible for creating depressed mood. More recent research suggests that there is indeed a subset of depressed people who have low levels of norepinephrine [3]. The main assumption of this hypothesis is that clinical depression is due to impairment of central monoaminergic function, a deficiency in the neurotransmission mediated by serotonin (5-HT, 5-hydroxytryptamin, norepinephrine (NA and dopamine (DA. The monoamine concentrations may be altered as a result of disrupted synthesis, storage or release, or the concentrations may be normal but the postsynaptic receptors and/or sub-cellular messenger activity may be impaired [4]. Serotonin's cell bodies are located in the midbrain raphe, and its axons project to frontal cortex where they may have important regulatory functions for mood, basal ganglia where limbic areas where they may modulate emotions, particularly anxiety. Serotonergic projections also arrive in the hypothalamus where they can regulate eating, appetite, and weight as well as sex drive and pleasure and regulate the sleep-wake cycle similar to serotonergic neurons, noradrenergic neurons project to frontal cortex to regulate mood, limbic hypothalamus for regulation of eating, appetite, weight, sex drive, and pleasure [5].

In addition, one unique norepinephrine projection to frontal cortex regulates cognition and attention, and another to cerebellum may modulate motor movement [6]. Likewise deficiencies in the activity of specific pathways for serotonin and norepinephrine have long been hypothesized to account for the symptoms of depression. Thus, depressed mood as well as problems concentrating may be linked to deficient functioning within the monoamine projections to frontal cortex, and emotional symptoms [7]. Hence, the treatment of depression is supposed to increase the availability of the amines in the brain. Different mechanisms may increase the availability of brain monoamines. These include blocking the reuptake of the monoamine in the synapse, inhibiting the intraneuronal metabolism of the monoamine or blocking the presynaptic inhibitory auto or heteroreceptors [8]. Monoamines affect a wide range of functions central in depression like sleep, vigilance, appetite, motivation, motor activity and reward and their imbalance may produce symptoms like aggression, euphoria and impulsiveness. Loss of interest or pleasure in activities that are normally pleasurable is one of the core symptoms of depression [9]. The brain dopaminergic system is crucially involved in reward behavior and/or motivation, especially the mesolimbic projections to the nucleus accumbens (NAc and prefrontal cortex. A reduced plasma concentration of Homovanilic acid (HVA, a dopamine metabolite, is found in depressed patients [3]. Research on the first antidepressants, monoamine Oxidase inhibitors (MAOI and Tricyclic antidepressants (TCA demonstrated their ability to facilitate noradrenergic and/or serotonergic neurotransmission, which correlated with behavioral excitation [10]. However, the non-specific action of TCAs reuptake

inhibition leads to a range of undesirable side effects. Both preclinical and clinical studies have clearly shown that selective reuptake inhibitors, e.g. acting on a single monoamine system, give a therapeutic advance. With the introduction of the selective serotonin reuptake inhibitors (SSRIs in the mid-1970s, a 5-HT-related hypothesis gained significance [11].

Today, the SSRIs are the most commonly prescribed antidepressants [12]. However, monoamine depletion in healthy individuals (control patients does not consistently produce depressive symptoms. Tryptophan (precursor of 5-HT depletion does not affect mood in healthy subjects, but does change mood in subjects with a history of psychiatric illness [13, 14]. In addition, tryptophan depletion produces alterations in rapid eye movement (REM sleep typical of depression whereas relapse into depression produced contrasting results in patients treated with SSRIs. Both serotonergic and noradrenergic compounds are useful in treating depressive patients. Some dopaminergic drugs have also been successfully in the treatment of depression. However, a rapid elevation of monoamines is not correlated with quick antidepressant action. Other brain chemicals may be involved in depression like neurokinins, aminobutyric acid (GABA, glutamate, neuroactive steroids, opioids, cholecystokinin, histamine and nicotine [14]. There is not clear evidence for one transmitter being central to the etiology of depression. The complex multifaceted nature of depression is made up of a variety of emotional, behavioral and cognitive elements. It is possible that each of these components of the syndrome may involve different neurobiological substrates.

Sleep alterations and depression

Sleep alterations is associated with affective disorders. The most common complaint of sleep disturbance in patients with major depression is insomnia. Difficulty falling asleep, frequent nocturnal awakenings, early morning awakening, non sleep, decreased total sleep, and disturbing dreams with more negative emotional content are often reported [15]. Objective sleep disturbances as assessed by polysomnographic recordings, confirm subjective experience in the majority of depressed patients. However, manifestation of most sleep abnormalities only occurs when depressive symptoms are present. Usually, sleep alterations in depression are grouped into three general categories.

1) Sleep continuity disturbances. Prolonged sleep latency, frequent arousals during sleep and early awakening in the morning. The sleep is more fragmentized which results in decreased sleep efficiency and reduced amount of sleep.
2) Slow wave sleep (SWS changes. SWS processes depression as indicated by a reduction of the SWS.
3) REM sleep changes. A reduced REM sleep latency (period of time from sleep onset to the first REM sleep period, prolonged duration of the first REM sleep episode, increased percentage of REM sleep and more frequent eye movements (increased REM sleep density during REM sleep are often reported in depression [15,16,17].

Depression usually leads to

- Difficulty getting to sleep
- Poor quality sleep
- Fewer Hours of sleep
- More awakenings during the night
- In severe cases, waking very early in the morning and being unable to get back to sleep
- Daytime tiredness

Another strong link between mood disorders and sleep is suggested by the observations that depressive symptoms are improved by sleep deprivation and reoccur after sleeping. A variety of sleep manipulations has been shown to have a rapid antidepressant effect. The ability of older antidepressants to suppress REM sleep was so striking that it was initially hypothesized that this ability was a mechanism of action of antidepressants. That some newer antidepressants, including moclobemide, nefazadone and bupropion, have proven antidepressant efficacy and may actually enhance REM sleep, has however scotched that theory. The melatonin MT1 and MT2 agonist and 5HT2C antagonist agomelatine, increases slow wave sleep and normalizes REM sleep in depression [15, 18]. Most antidepressants enhance central monoaminergic activity, especially serotonergic activity. Serotonin modulates sleep and wakefulness [18].

Hypothesis of the pathophysiology of depression

An evolving hypothesis of the pathophysiology and treatment of depression involves adaptation or plasticity of neural systems. Neuronal plasticity or remodeling is a fundamental concept that underlies central nervous system function as it relates to many types of experience [2, 11]. Simply, neuronal plasticity is the ability to acquire information and make the appropriate responses to the same or related future stimuli. This includes sensory, cognitive, emotional, social, as well as endocrine inputs and combinations of this information. Therefore, it is likely that plasticity or remodeling also plays a significant role in the patho- physiology and treatment of major psychiatric illnesses, such as mood disorders [19].

Neuronal atrophy is demonstrated by a decrease in the number and length of branch points of the apical dendrites of CA3 neurons [2, 19]. Repeated stress is reported to cause atrophy of CA3 pyramidal neurons in the hippocampus, including a decrease in the number and length of apical dendrites. In addition, exposure to acute stress decreases the proliferation of cells in the dentate gyrus of the hippocampus [20]. Death of CA3 neurons has been reported to occur in response to severe and long-term stress or glucocorticoid treatment.

These reports of atrophy and cell death in stress and depression raise the possibility that the action of antidepressants may involve reversal or blockade of these effects or direct regulation of synaptic architecture, dendritic morphology, and survival of neurons. The influence of antidepressant treatment on the atrophy of CA3 pyramidal neurons has been examined by McEwen and colleagues. Their studies demonstrate that administration of an atypical antidepressant (Tianeptine, but not a 5-HT selective reuptake inhibitor (Fluoxetine, blocks the stress-induced atrophy of CA3 pyramidal cells [21].

Stress is reported to decrease the birth or neurogenesis of these cells in adult animals. Although the capacity for new cell birth is not observed in most regions of the mature nervous system, the dentate gyrus is one of the few areas where adult neurogenesis has been demonstrated. Normal rates of neurogenesis, as well as death of granule cells, are dependent on physiological concentrations of glucocorticoids; however, acute stress or exposure to high levels of glucocorticoid decreases neurogenesis of granule cells [22].

Two recent studies report that the numbers of cells in prefrontal cortex are decreased in patients with depression. The first of these studies reports a reduction in the number of glia, but not neurons, in the subgenual prefrontal cortex of patients with major depressive disorder or bipolar disorder. Second study has reported a decrease in neuronal size and the number of neurons and glia in the prefrontal and rostral orbitofrontal cortex [2, 22, and 23]. These findings suggest that atrophy and survival of neurons may also contribute to certain symptoms of depression, such as depressed mood and working memory that can be attributed to prefrontal cortex. Neurons may also contribute to certain symptoms of depression, such as depressed mood and working memory, which can be attributed to prefrontal cortex [24].

Antidepressant treatment could oppose the actions of stress is via up regulation of the neurogenesis of dentate gyrus granule neurons. Preliminary studies from our laboratory indicate that chronic, but not acute, antidepressant treatment increases neurogenesis of hippocampal granule cells [25, 26].

Glucocorticoids and depression

There is a large literature which demonstrates that corticosteroids can influence neurotransmitter tone and, vice versa, that corticosteroid secretion is regulated by the neurotransmitters implicated in depression. Accordingly, much attention in the field

has been focused on brain areas showing high levels of corticosteroid receptor expression, namely the hippocampus, and more recently, the prefrontal cortex. These two brain areas, which are reciprocally connected, exert inhibitory neural control over the hypothalamo–pituitary–adrenal (HPA axis, and thus restrain excess corticosteroid secretion [14, 26].

M. Kawata et al in 2001, review on depression associated hypercortisolism results from impairments to the neural and endocrine mechanisms governing GC negative feedback in the limbic–hypothalamic–pituitary– adrenal (LHPA axis. Depending on the intensity or duration of the stress, as well as individual qualities (genetics, psychological state, etc., the endocrine response to stress which is supposed to be adaptive becomes pathological the organism loses its ability to switch the HPA axis off and the hypersecretion of GC continues unabated. As mentioned above, impaired GC negative feedback seems to be a hallmark of depression [27, 29].

The neurotrophic hypothesis of depression

The neurotrophic hypothesis of depression states that a deficiency in neurotrophic support development of depression and that reversal of this deficiency by antidepressant treatments may contribute to the resolution of depressive symptoms. Work on this hypothesis has focused on brain -derived neurotrophic factor (BDNF, one of the most prevalent neurotrophic factors in adult brain [27]. Acute and chronic stress decreases levels of BDNF expression in the dengyrus and pyramidal cell layer of hippocampus in rodents. This reduction appears to be mediated partly via stress such as stress-induced increases in serotonergic transmission. Conversely, chronic (but not acute administration of virtually all classes of antidepressant treatments increases BDNF expression in these regions and can prevent the stress-induced decreases in BDNF levels. There is also evidence that antidepressants increase hippocampal BDNF levels in humans. Antidepressants produce the opposite effects they increase dendritic arborizations and BDNF expression of these hippocampal neurons. It is possible that the down regulation of BDNF may contribute to the atrophy of CA3 neurons and reduced neurogenesis of granule cells in the hippocampus, although elevated levels of adrenal glucocorticoids could also account for these effects [2, 28, 29].

R. S. Duman et al.in 1999, demonstrated that up-regulation of BDNF may be involved in the actions of antidepressant treatment and that decreased expression of this neurotrophic factor could contribute to the negative influence of stress on certain neuronal systems. A role for BDNF in the action of antidepressant treatment is supported by several lines of evidence. First, we have found that chronic administration of different classes of antidepressants increases the expression of BDNF in limbic brain regions, particularly the hippocampus. These studies also demonstrate that antidepressant pretreatment blocks the down-regulation of BDNF in response to stress. Second, direct application of BDNF into the midbrain of rats is reported to have antidepressant effects in behavioral models of depression, including the forced swim and learned helplessness paradigms. Third, BDNF is reported to be a potent neurotrophic factor for both the NE and 5-HT neurotransmitter systems. These findings demonstrate that BDNF is a target of the cAMP system and antidepressant treatment and that BDNF is sufficient to produce an antidepressant response. Moreover, the results suggest that BDNF could influence monoamine systems via actions at either presynaptic sites (e.g.increased function of monoamine neurons or postsynaptic sites (e.g. increased output of target neurons [20, 29].

HPA axis overdrive and depression

H.M.Van Praag in 2004, reviwed on many additional data indicate that the HPA system may be hyperactive in depression.

Pertinent are the following observations

- Increased level of circulating ACTH.
- Increased urinary cortisol excretion.
- Increased levels of CRH in CSF and an increased number of CRH secreting neurons and CRH messenger RNA in the hypothalamus. The number of CRH binding sites on the other hand is reduced, possibly consequent to elevation of CRH availability.
- The number of neurons containing both CRH and vasopressin is increased and so is the number of neurons that produce vasopressin or oxytocin only. Plasma levels of arginine vasopressin (AVP were found to be elevated in depression. Both vasopressin and oxytocin potentiate CRH-mediated ACTH release GR binding on blood platelets and in postmortem brain is decreased, indicating that GR negative feedback is diminished [24,25].

Hypothyroidism and depression

An enormous research effort over the last 50 years failed to achieve this goal but, nonetheless, produced some important findings. First, the vast majority of patients with major depression are euthyroid. Second, basal peripheral thyroid hormone levels are not particularly informative, although subjects with depression have higher mean Thyroxine (T4 levels compared with when they are remitted and also compared with healthy control subjects. Moreover, significant decreases in T4 levels occur with response to various treatments, including antidepressant drugs. The consistent observations about the thyroid and depression reported in both the psychiatric and endocrine literature, interest in the thyroid as a major factor in the biology of depression has waned, and the thyroid axis has received little attention in current models of the etiology of depression. Thyroid hormones have been shown to potentiate antidepressant response in treatment-resistant depression. This has been observed particularly for T3 but also for T4 [30, 31].

Emotionality and altered activity in depression

Depressed mood, feelings of worthlessness, inappropriate guilt and suicidal thoughts are some of the most frequently reported affective changes in depressed patients. These symptoms of increased emotionality are mainly described verbally by the subjects. However, changes in emotionality can, at some degree, be reflected in presence of abnormal activity. The changes are often seen as psychomotor agitation, slowness of motor activity or alteration in novelty-induced behavior reflecting anxiety, fatigue or increased harm avoidance. Psychomotor retardation, slowness of movement, is nearly an opposite motor disturbance that can be among the earliest symptoms of depression [31, 32]. The important brain regions that regulate locomotor activity, the striatum and the cerebellum, receive extensive monoaminergic input. Serotonergic and dopaminergic nuclei project to both, whereas noradrenergic nuclei project to the cerebellum only. An impairment of these neurotransmitter systems may be the basis of the locomotor alterations observed in depressed patients. Learned helplessness theory points to motivational, cognitive, and emotional deficits as characteristic of depression, also from a cognitive-behavioral perspective, sadness or melancholy can be conceptualized as the emotion associated with loss of contact with a positive reinforcer; that is, loss of a valued relationship, object, or state ([30, 31, 32, 33]. Similarly, happiness or joy is the emotion associated with contact with a positive reinforcer. And depression is characterized by negative behavioral and cognitive features that are highly disruptive to functioning and rather than being only temporarily debilitating, the behavioral disruption in depression is recurring.

Lang (1985 reports consistent findings that emotional states are highly Interco related and fall along three bipolar dimensions: intensity of arousal, valence (approach–avoidance behavior, and behavioral control–disruption. He suggests that the different findings may be reconciled by viewing emotions fundamentally as behavioral acts in the sense that "specific actions have their own physiological and behavioral topography" [34]. In addition, emotionality has been shown to correlate with an increased ambulatory blood pressure and heart rate. Emotional individuals show higher levels of perceived daily stress, trait anxiety and depressive symptoms [35]. These symptoms can be objectively measured in animal models of depression e.g. using an open field test to measure changes in locomotor activity, novelty-induced and exploratory behavior and harm avoidance. A diminished motivation

is a core symptom of clinical depression that can be manifested by alterations of sexual function. Similarly, rodents subjected to procedures that induce a depressive-like state exhibit impairment of sexual drive (i.e., latency and frequency of mounts, intromission and ejaculation [36].

CONCLUSION

The hypothesis of depression has dominated our understanding of depression and of pharmacological approaches to its management and it has produced several generations of antidepressant agents, ranging from the monoamine Oxidase inhibitors (MAOIs, through Tricyclics (TCAs and selective serotonin reuptake inhibitors (SSRIs, to the recently introduced selective Noradrenaline reuptake inhibitor (NARI, Reboxetine. This hypothesis was based on a correlation of the psychological and cellular actions of a variety of psychotropic agents. Other biogenic amines in the brain have also been linked to depression with the development of monoamine or biogenic amine hypothesis.

REFERENCES

1. Osborne FX. Almeida et al. SMAD pathway mediation of BDNF and TGFβ2 regulation of proliferation and differentiation of hippocampal granule neurons. The Company of Biologists 2005;132 :3231-3242.
2. Duman RS. Pathophysiology of depression: the concept of synaptic plasticity, European Psychiatry. 2002; 17 Suppl 3 :306-10.
3. Altshuler L, Kiriakos L et al. The impact of antidepressant discontinuation versus antidepressant continuation on 1-year risk for relapse of bipolar depression: a retrospective chart review. J Clin Psychiatry 2001; 62(8 :612-6**.**
4. Hindmarch I. Expanding the horizons of depression: beyond the monoamine hypothesis. Psychopharmacol 2001; 16: 203-218.
5. Gerard J. Tortora and Sandra Reynolds Grabowski. Principles of Anatomy and Physiology, 10th ed. John Wiley & Sons, Inc ; 2006.
6. Katzung GH. Basic & clinical Pharmacology; 9th ed. 2004: 482-496.
7. Stephen M. Stahl. Depression and bipolar disorder: Stahl's essential psychopharmacology. Cambridge University Press; 2004.
8. Kiss J. Theory of active antidepressants: A nonsynaptic approach to the treatment of depression, Neurochemistry International 2008; 52 :34–39.
9. Victor I. Reus, Ed., Mental Disorders in Harrison's, Principles of Internal medicine, 16th Ed, 2007 :2552-2556.
10. Hippius H, and Winokur G, Pschopharmacology of mood disorders In, Clinical
11. Psychopharmacology I, part-2:86-93
12. Richard A. Helms, Eric T.Depression. In Harfindel the text book of Therapeutic drug and disease management, 8th ed. Lippin coat Williams and wilkin business: 2006.
13. Linda G. The Biology of Antidepressants, Annals of Family Medicine 2005; 3:449-456.
14. Jack D Barchas and Margaret A, Biochemical Hypotheses of Mood and Anxiety Disorders. Basic Neurochemistry 2006.
15. Rang HP, Dale MM, Ritter JM. Drugs used in affective disorders in Pharmacology 1999.
16. Michael Berk. Sleep and depression - theory and practice, In: Documents for small business and professions; 2009.
17. Kupfer DJ. Sleep research in depressive illness: Clinical implications: a tasting menu, Biol. Psychiatry 1995; 38 :391–403.
18. Tripathi KD, Essentials of medical pharmacology, 5th ed, New Delhi: Jaypee Brithers medical publishers Pvt. Ltd; 2003:425
19. Gold PW, Goodwin FK, Chrousos GP. Clinical and biochemical manifestations of depression (two parts, N. Engl. J. Med. 1988; 319: 348–420.
20. Eugene CT, John T, Patlan Jr, Fabrizia. Diabetes mellitus. In Harrison's principle of internal medicine, 16th ed, Mc graw- Hill medical publishing division; 2005: p.2152-2185.
21. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch. Gen. Psychiatry 1997; 54 :597–606.
22. Sendtner, Michael. Molecular mechanisms in spinal muscular atrophy models and perspectives, Current Opinion in Neurology 2001;14 :629-634.
23. Liu CC, Liang KY, Liao SC. Antidepressant-associated mania. Soon after switch from Fluoxetine to Mirtazapine in an elderly woman with mixed depressive features. Journal of psychopharmacology 2009; 23 :220–222.
24. Lu XY. The leptin hypothesis of depression: a potential link between mood disorders and obesity? Current Opinion on Pharmacoogy 2007; 7 :648–652.
25. Praag HM. Can stress cause depression? Progress in Neuro-Psychopharmacology & Biological Psychiatry 2004;28 :891– 907.
26. Plotsky PM, Owens MJ, and Nemeroff CB. Psychoneuroendocrinology of depression: hypothalamic-pituitary-adrenal axis.Psychiatric Clinics of North America 1998;2 :293–307.
27. Mirescu C and Gould E. Stress and adult neurogenesis, Hippocampus 2006; 16 :233–238.
28. Victor I. Reus Ed. Mental Disorders in Harrison's, Principles of Internal medicine, 16th ed :2552-2556.
29. Yu S, Holsboer, Osborne FX, Almeida. Neuronal actions of glucocorticoids: Focus on depression. J Steroid Biochemistry & Molecular Biology 2008; 128: 300–309.
30. Kawata M. et al. Stress and Corticosteroid Receptors. PTSD Brain Mechanisms and Clinical Implications, Springer Japan; 2007: 29-36.
31. Mason GF, Anand A, Sanacora G, Epperson N, Haga K, Appel M, Goddard AW, Charney DS, et al. Different Relationships among Cortical Amino Acids in Unipolar and Bipolar Depression. Proc. Intl. Soc. Mag. Reson. Med 2001;9 :557.
32. Joffe T. Is the thyroid still important in major depression? J Psychiatry Neurosci 2006;31 :367-8.
33. Nestler J, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia, LM. Neurobiology of Depression. Neuron 2002;34 :13–25.
34. Allen NB and Badcock PB. Darwinian models of depression: a review of evolutionary accounts of mood and mood disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2006;30 :815–826.
35. American Psychiatric Association.Diagnostic and Statistical Manual of Mental
36. Disorders (DSM-IV.4th Edition: American Psychiatric Press Inc, Washington
37. DC, USA; 2000.
38. Practice Guideline for Major Depressive Disorder in Adults. Washington, D.C.: American Psychiatric Association; 1993.
39. Lang T et al. mental integrity and emotional treatment across disorder: using examples of depression. Cognition behavior therapy 2009; 38: 21-28.