Review Article

RATIONALE OF DEPRESSION AND PURPOSE OF ANTIDEPRESSANT DRUGS: A REVIEW

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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 a consequence of altered regulation of particular brain chemicals. In addition, the present article reviews the evidence from both clinical and experimental studies which implicates rationale of depression and the mechanism from which antidepressant drug act for the maintenance of depressive illness. Present studies evolving rationale of the pathophysiology, catecholamine, Sleep alterations, Glucocorticoids, the Neurotrophic, Hypothyroidism, Emotionality and altered activity in depression and treatment of depression involves adaptation of neural systems. This rationale 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: Depression, Information processing, adaptation, Antidepressant.

INTRODUCTION

Depression is one of the most debilitating disorders of our times. Depression is characterized by extended periods of dysphasia, feelings of meaninglessness and hopelessness. Many patients suffering from depression are also afflicted with anxiety. Anxiety can be described as a group on non-specific unpleasant symptoms which are similar to the reactions to horror and fear. The threat can be experienced by the patient as external or internal. Conditions counted as belonging to the sphere of anxiety are phobias, panic attacks, compulsive thoughts and compulsive actions. Antidepressant medication, one of the most common (and often first-line) treatments to date, aim to alleviate symptoms, but finding which type of drug benefits which patient remains a daunting task. The underlying mechanism that translates neurochemical effects to symptom improvement is still far from precise. The evidence on the effects of antidepressants on brain systems and cognitive functioning, and examined the possible value of these correlates as predictors of response¹. Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and physical well-being. Depression is an etiologically heterogeneous group of brain disorders characterized by a wide range of symptoms that reflect alterations in cognitive, psychomotor and emotional processes^{2,3}.

Studies using acute (or sub-chronic) antidepressant administrations in healthy subjects showed effects on affective cognition. In depressed patients, neuroimaging studies examining the effects of antidepressants in pre-post designs have shown changes in the activation of the anterior cingulate cortex and the limbic system after treatment. Increasing evidence shows that baseline anterior cingulate cortex activation could be a possibly critical biomarker of treatment

response. The few studies performed to date also indicate potentially different pathways for antidepressants targeting the serotonergic neurotransmitter system versus those targeting the noradrenergic one, but findings are not always consistent. More studies are necessary to establish whether early cognitive effects of drugs are predictive of long-term efficacy in depressed patients. Considering the heterogeneity of depression and in order to approach a more personalized treatment, future studies should also elucidate the effects of antidepressants on different cognitive systems and subsequently on different symptom profiles. A treatment for depression that affects up to 20% and causes an enormous burden for the society^{4,5} is far from ideal, and often inadequate. Fewer than 50% of patients with depression achieve full remission with optimized treatment. Despite the increase in the available therapeutic armamentarium⁴, in particular selective serotonin (5-HT) reuptake inhibitors (SSRIs) and serotonin-noradrenalin (NA) reuptake inhibitors (SNRIs), 50% of depressed patients remain untreated.

In addition to the need to administer the drugs for weeks or months before seeing clinical benefit, side effects are still a serious problem even with the newer medications. A substantial number of patients discontinue antidepressant treatment during the first weeks of treatment, and poor compliance remains one of the most common obstacles of antidepressant treatment⁶. The SSRIs are relatively well tolerated compared with tricyclic, imipramine-type, antidepressants, but they also cause some adverse effects linked to their actions on gastrointestinal tract, sexual functioning and sleep patterns⁷. A withdrawal syndrome on stopping treatment has also been reported with the use of some SSRIs. There is still a great need for faster acting, safer and better tolerated and more effective treatments for depression, as such treatments could lead to more complete

remission in more patients⁸. To this aim, the field has to move beyond today's mechanisms of antidepressant medications, as it is now well recognized that synaptic facilitation and augmentation of the levels and effects of NA and 5-HT only partially explain the action of current antidepressants. There is now an accumulation of knowledge derived from animal studies about non monoamine systems that might contribute to the pathophysiology of depression and human evidence in support of this concept is increasingly available. Among the various strategies to help patients with new, more effective and better tolerated treatments, the re-synchronization of biological rhythms appears to be particularly attractive given that a disruption of circadian rhythms is characteristic of a large number of mood disorders^{4,9}.

CATECHOLAMINE RATIONALE

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 nor epinephrine (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 nor epinephrine^{1,10}. 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 impaired¹¹. 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. Today, the SSRIs are the most commonly prescribed antidepressants¹². 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^{1,13,14}. 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^{1,14}. 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 are 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^{1,15}. 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 fragmented 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)^{1,15,16,17}.

RATIONALE 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^{18,19}. 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 pathophysiology and treatment of major psychiatric illnesses, such as mood disorders^{1,20}.

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^{21,22}. 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^{1,23,24}.

THE NEUROTROPHIC RATIONALE 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 brain²³. Acute and chronic stress decreases levels of BDNF expression in the dent gyrus 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^{1, 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^{1, 22, 26}.

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.

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