NOVEL APPROACHES TO THE THERAPY OF DEPRESSION

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Summary

Conventional therapy of depression is centred on increasing availability of synaptic neurotransmitters. It comes along various drawbacks arising from non selectivity of these drugs leading to other histaminergic and adrenergic side effects and blocking post-synaptic receptor sites of cholinergic (muscarinic), histaminergic, adrenergic receptors; even severe consequences like desensitisation and down regulation of receptors. This article focus on various newer therapeutic agents belonging to diversified categories, which can be blended with conventional therapy of depression there by increasing the efficacy of in combinational way.

Key words: 5-HT, Allopregnenolone, Depression, Glucocorticoid antagonist, Neuropeptide Y, Nitric oxide synthase inhibitors, Tryptophan

Introduction

Depression is a syndrome or collection of symptoms which occur together with sufficient frequency to constitute a recognizable clinical condition. The most common symptoms are apathy, fatigue, depressed mood, depressive thought content and diminished concentration. Theoretical approaches to treatment of depression tend to be either strongly biological or strongly psychological in nature. It is now clear that a variety of different factors are implicated in the etiology of depression. Existing drugs have undesirable side-effects which reduce compliance with therapy and significant numbers of antidepressants do not make a satisfactory response(1-2). No doubt that new antidepressants are needed.

Major neurotransmitters known to be involved in pathology of depression are namely norepinephrine, serotonin and dopamine. It is the depletion of these neurotransmitters from certain regions of the brain such as the hypothalamus, amygdala, and cortical areas involved in cognition and other high processes, have a great impact in contributing to depression. It is also observed that patients with suicidal tendencies show prominently low levels of serotonin and norepinephrine which is one of the symptoms of depression (3).

Stress and 5HT receptors

Numbers of studies have shown that brain of depressed patients and suicide victims have shown increased expression of $5HT_{2A}$ receptors, which are presynaptic (responsible for reuptake of 5-HT). Immunolabelling studies in chronically depressed rats have shown that $5HT_{2A}$ receptors are increased in frontal cortex and decreased in hippocampus and hypothalamus of rat brain (4). In rats receiving chronic predictable stress, $5HT_{1A}$ agonists like 8-OH DAPT is not fully active as antidepressant indicating the down regulation of $5HT_{1A}$ receptors. All these evidences confirms that chronic stress induced depression is attributed to up-regulation of $5HT_{2A}$ receptors and down regulation of $5HT_{1A}$ receptors in the brain (5). Such cases hardly respond to any drug treatment as receptors are insufficient in number to show pharmacological action.

Conventional therapy of depression is associated with number of side effects due to chronic administration of TCAs or MAOIs which decrease responsiveness and/or the number of postsynaptic receptor sites.(i.e. desensitization and down regulation) and causing additional side effects sedation, weight gain, and hypotension. In the elderly, this is a particular problem, since it can result in fainting or falls (6). Following are some of the newer therapeutic regimens which can be further developed and can be involved in efficient treatment of depression.

Nitric oxide synthase inhibitors

Presently in the findings of novel antidepressant the nitric oxide synthase inhibitors are coming in the focus. In last 5 to 6 years many studies have been carried out on the nitric oxide synthase inhibitors which give antidepressant-like activity (7). Nitric oxide, a messenger molecule in the brain, synthesized from L-arginine by nitric oxide synthase (NOS), has been implicated in neurotransmission, synaptic plasticity, learning, and perception of pain, aggression and depression (8). Nitric oxide synthase (NOS) is the NO converting enzyme.

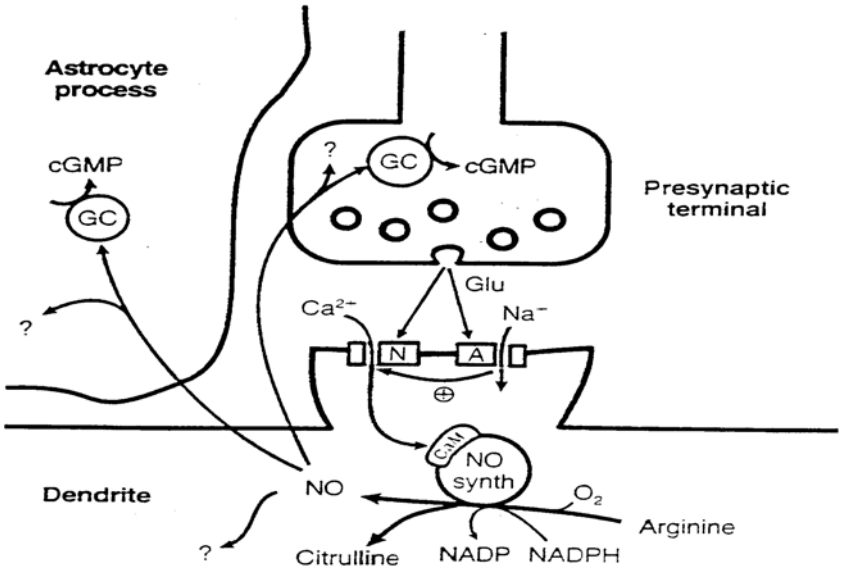

Figure I : **Production of nitric oxide (NO) in the CNS.**

Figure I shows NO formation stimulated by postsynaptic glutamate receptor activation. Activation of the NMDA receptor depolarizes the cell and subsequently results in an influx in Ca^{2+} ions into the postsynaptic cell. The calcium ions bind to calmodulin and activate the NO converting enzyme nitric oxide synthase (NOS). NOS stimulate the conversion of L-arginine to NO. NO then diffuses across the synaptic cleft to the presynaptic membrane where it activates guanylate cyclase. Guanylate cyclase stimulates guanosine monophosphate (cGMP), which is responsible for the neuroadaptive changes mediated by NO.

L-arginine-nitric oxide (NO)-cyclic guanosine monophosphate is an important signaling pathway that is reported to be involved in depression (9). Recent evidences have shown that the reduction of nitric oxide levels within the hippocampus can induce antidepressant like effects, thus implicating endogenous hippocampal nitric oxide in the neurobiology of stress and depression (10). Nitric oxide is also known to modulate the levels of cyclic guanosine monophosphate which in turn is known to produce depression like state in animals (11).

Studies have shown the possibility that the inhibition of nitric oxide synthase enzyme could be used as a strategy to enhance the clinical efficacy of serotonergic antidepressants. Further studies have shown that endogenous nitric oxide may exert a negative control over the levels of serotonin and dopamine in the hippocampus (12).

Cytokines and glucocorticoids

Recent studies have shown that cytokine administration to laboratory animals induced a wide range of behavioral effects like psychomotor retardation, reduced food intake, decreased interest in daily activities, sleep disturbances, alteration in learning and memory and anhedonia resembling the symptoms of depression. Although these effects are usually studied in animals acutely injected with cytokines, there is evidence that they also occur during chronic immune activation, whether the treatment is administered repeatedly or animals are chronically infected. The cytokines proved to be involved in the depression are IL1, IL2, IL6 and TNF-α. The reason underlying this cytokine induced depression is activation of Hypothalamus- Pituitary- Adrenal (HPA) axis. Activation of HPA axis not only induces depressive symptoms but also reduces negative feedback to the glucocorticoid levels, as these levels are generally increased in depressed patients (13).

This increase in glucocorticoid levels is an attribute of downregulation of certain serotonergic receptors such as $5HT_{1A}$ receptors in the brain. Glucocorticoid levels may therefore play a role of marker in understanding the depression (14).

Indoleamine-2,3-dioxygenase (IDO) and tryptophan dioxygenase (TDO) inhibitors

Trytpophan availability plays a role in cytokine induced depressive symptoms. Tryptophan is precursor for the biosynthesis of serotonin. Tryptophan (TRP) degradation into kynurenine (KYN) by the enzyme, indoleamine-2,3-dioxygenase is increased during immune activation by interferon (IFN) therapy.

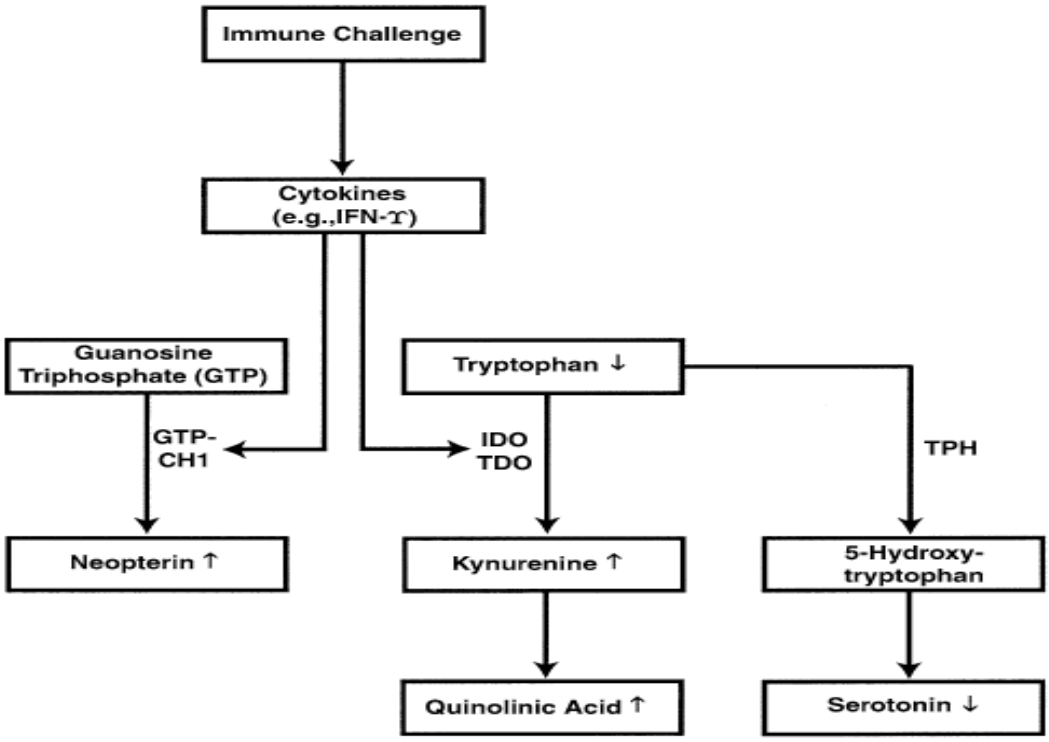

Figure II: Tryptophan metabolism and neopterin synthesis upon immune system activation.

Fig II: shows that cytokines (e.g., interferon [IFN]-) induce the enzyme indoleamine-2,3-dioxygenase (IDO) that catabolizes tryptophan into kynurenine and then quinolinic acid, thereby reducing the availability of tryptophan for serotonin synthesis via the enzyme tryptophan hydroxylase (TPH). The activation of the kynurenine pathway may also be due to the induction of the liver enzyme tryptophan dioxygenase (TDO) by cytokines. Cytokines induce neopterin synthesis from activated monocytes/macrophages by activating guanosine triphosphate cyclohydrolase 1 (GTP-CH1), an enzyme that catalyzes the formation of neopterin from guanosine triphosphate (GTP) (15).

In this way, the newer therapeutic area may target over the inhibition of metabolism of Tryptophan into Kynurenin by inhibiting the enzymes like indoleamine-2,3-dioxygenase (IDO) and tryptophan dioxygenase (TDO).

5-HT and neuropeptide Y

It is widely believed that the reduction of 5-hydroxy-tryptamine (5-HT) and neuropeptide (NPY) neurotransmission or receptor expression enhances or leads to depression. This notion is also supported by recent studies showing that chronic stress treated rats displayed a significant decrease in the expression of 5-HT and NPY in the rat hippocampus. These lines of evidence focus on hypothesis that

reduced 5-HT and NPY neurotransmission in the hippocampus made significant contributions to chronic unpredictable mild stress-induced depression in rats. Therefore intra-hippocampal microinjection delivery of NPY and 5-HT can provide the therapeutic benefits in depressed patient (16).

Corticosteroids

Corticosteroids are secreted by adrenal gland in response to stress and modulate neuronal activity in the hippocampus that is related to behaviour adaptation. This functioning of neuronal circuits in hippocampus is also under the control of 5-HT_{-1A} receptor expression as these receptors are dominant in hippocampus region. Corticosteroids suppress 5-HT_{-1A} receptor expression in specific areas of hippocampus in rhodents (17). Separate series of experiments have shown that ketoconazole, which is glucocorticoid receptor antagonist, produced antidepressant-like behavioral changes in swimming, highlighting a serotonergic mechanism. Thus glucocorticoid receptor antagonists will provide a separate room for developing the effective combinational therapy for depression (18).

Allopregnanolone, also known as 3α,5α-tetrahydroprogesterone or THP, is an important neurosteroid in the human brain. It is a metabolite of progesterone and a barbiturate-like modulator of central GABA receptors that modify a range of behaviors, including the stress response. This drug minimizes brain damage, reduces or eliminates post-traumatic epileptic seizures, and improves patients psychological functioning and overall quality of life. Desipramine in combination with allopregnanolone increased climbing behaviour in forced swim test arguing a role for noradrenergic or dopaminergic effects. The combination of fluoxetine and desipramine synergized with subthreshold doses of allopregnanolone and produced a change in climbing behavior only, indicating involvement of dopaminergic pathways prominently (and not the serotonergic pathways). However the underlying mechanism of action still remains unclear (19) Thus allopregnenolone in combination with standard antidepressants will help to improve the efficacy of the therapy of depression.

Role of Repeated Electroconvulsive Treatment:

Studies have revealed that repetitive electroconvulsive shock (ECS) treatment induces two humoral factors in mouse, which are responsible for occurrence of antidepressant effect when tested in forced swim test. Serum of mice, which are repeatedly treated with very mild electroconvulsive shock, showed considerable levels of glycolipid having composition GalNAcα1-3GalNAc and a peptide that is known as mouse fibrinopeptide-A (sequence: TDTEKDGEFLSEGGGV). These factors are supposed cross the blood brain barrier during ECS treatment and reach hypothalamus where it gives antidepressant activity. Antidepressant activity of these humoral factors was found to be reversed by dopamine antagonist in dose dependant manner indicating involvement of dopaminergic system in its antidepressant action. However exact mechanism of action remained unrevealed (20).

Previously, some of the studies have also demonstrated the usefulness of electroshock treatment in the depression therapy. Further studies may help to improve and implement this therapy in mainstream regimen of depression.

The existing therapy for depression needs to focus on newer targets. All the conventional therapies are aimed towards increasing availability of neurotransmitters at the synaptic levels, but no therapy exists till date, which acts by the up regulation of prime receptors that are involved in pathophysiology of depression ($5HT_{1A}$). The ways that can be employed in upregulation of this receptor should be found out. Number of endogenous substances and hormones govern the balance of these receptors and these hormone levels in turn are governed by these receptor expression and regulation. Similarly there are other ways to improve efficacy of present depression treatment by involving number of other strategies. Considering this fact, there might be some ways by which the receptors that are involved in etiology of depression can be upregulated:

1] Carefully maintaining the levels of those endogenous substances which in turn maintain the normal receptor regulation by maintaining corticosteroids and mineralocorticoid levels and by controlling production of cytokines and interlukins (especially in patients on interlukin therapy and autoimmune diseases).

2] Introduction of the agent, which may not be having direct antidepressant action, but will help to prohibit or minimize the down regulation of the essential receptors and thereby increasing the availability of neurotransmitters like glucocorticoid receptor antagonist, indoleamine-2,3-dioxygenase (IDO/ TDO) Inhibitors, Nitric oxide synthase inhibitors

3] Developing newer techniques which will focus on up-regulation of these receptors and improve efficacy of treatment such as intra-hippocampal delivery of Neuropeptide Y, Alopregnenolone in combination with tricyclic antidepressants.

4] Implementation of other therapeutic techniques with appropriate optimization in order to supplement the mainstream therapy like mild Electroconvulsive shock treatment.

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