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Treatment of Mental Disorders : Recent Advances in Neurochemistry

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Abstract

The diverse neurobiological nature of mental disorders has attracted the attention of interdisciplinary researchers and considerable progress has been made over the last 2 to 3 decades in developing suitable therapy. In spite of adding newer drugs every year, certain mental disorders still remain to be complex psychiatric social problems not fully attended to. However, recent developments in research strategies like cell culture, PET, cloning, receptor mediated signal transduction and molecular biology have greatly advanced our capacity to treat mental illness with newer drug with less toxicity and fewer side effects. These approaches towards treatment of certain mental disorders are highlighted in this article.

Key words -

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The past 50 years, more so the last two decades, have seen a phenomenal growth in neurosciences, both basic and clinical, so much so this decade has been described as the "decade of brain". The progress in Neurochemistry, neuronal mapping, receptor identification and cloning and development of receptor specific drugs has been the hall mark of success in combating psychiatric illnesses.

The fact that the abnormality of brain chemistry results in mental illness was supported by experimental results as early as 1940. The development of schizophrenic like symptoms in healthy subject by LSD, amphetamine and mescaline supported this view. The action of antipsychotics by blocking dopamine (DA) receptor led to establish the dopaminegic hypersensitivity theory in schizophrenia.

Ligand binding techniques and molecular biological approaches have helped in visualizing the interaction of drugs more

intimately. PET studies have strengthened the correlation between dose and efficacy of antipsychotics. The knowledge that antipsychotics block DA receptors and produce extra pyramidal symptoms has influenced the development of new antipsychotic drugs.

It is now certain that, taken together, mental illness and the abuse of alcohol and other drugs are among the most widespread, destructive and costly health problems facing man kind today. According to experts, mental disorders are of same magnitude as cancer and heart disease. Mood disorders including depression and manias viewed as "diseases of the substances of the brain" by Hippocrates, were considered to be of biological occurrence only in later half of 20th century [1], [2], [3].

Schildkratut [4], in his review, suggested the link between the affective disorders and biogenic amine metabolism in CNS. The evidence was available from the pharmacological studies with reserpine, amphetamine, MAO - inhibitors and the early tricyclic antidepressants, imipramine and amitriptyline. Although the catecholamine hypothesis was over simplification of complex biological state, this formed the basis of neurochemical research on mood disorders. These studies, have been extended to include serotonin, dopamine (DA), GABA and numerous neuropeptides. More recently the investigations have involved molecular biochemical studies, pharmacological challenges and elucidation of receptor functions. Further, molecular genetics is also under intensive scrutiny. These studies have focused on to understand not only the variability of potency, efficacy and proficiency of a gamut of drugs used in this complex 'biological state', but also tried to understand the pharmacokinetics of drugs at molecular level and to develop new drugs.

The diverse neurobiological nature of these disorders has attracted the attention of interdisciplinary researchers and considerable progress has been made over the last 2 to 3 decades in developing suitable treatment for them.

In spite of adding dozens of new drugs every year, certain mental disorders, like depression, still remain to be a complex psychiatric social problem not fully attended to. Although considerable advances have been made with nearly 18-20 antidepressant compounds being available, no one agent has demonstrated greater efficacy than another. Currently available data suggests that only 20-40% of patients entered into treatment regimen reach full recovery, while 20% do not respond and remain chronically ill. So the development of more efficacious agent that will produce complete remissions in patients, especially in non responders, is a major challenge.

Unlike many other illnesses, there is no medical laboratory test that has the necessary sensitivity and specificity to reliably diagnose the mental disorders. Several biological abnormalities, including hyperactive hypothalamo-pituitary-adrenal system, blunted TSH response to TRH and decrease in 5-HT metabolites in CSF, among others, have been tried in sub population of patients [5]. Regulations of 5-HT2 receptors in platelets has also been tried without success [6]. Apart from the tricyclic antidepressants, MAO-inhibitors and atypical antidepressants, most recently the selective serotonin reuptake inhibitors (SSRI), like fluoxetine, paroxetine and setraline have been used in depression.

As of now, no biological or clinical predictors of treatment response reliably serve as a guide to its efficacy. Although these therapeutic agents have greatly advanced our capacity to treat mental illness and despite the fact that newer antidepressant medications have been developed with less toxicity and fewer side effects, future advances are still needed.

The "too little or too much" phase of affective disorder has to be broadened and studies should be more beyond this phase. Increasing research strategies like PET, utilization cell cultures from human subjects, signal transduction measures and the molecular biology have yet to be systematically applied.

Most clinical investigations of plasma norepinephrine (NE) reveal some degree of increase, which is interpreted as evidence of increased peripheral sympathetic nervous system activity in depressives. NE is increased in unipolar depression with melancholia [7]. Highly variable results have been reported with plasma MHPG levels with no change in CSF MHPG level have been reported earlier. Metabolites of NE have been studied in depressed patients without much success. Recently adrenergic receptors have been most extensively studied in blood cells and platelets. No significant difference in maximum binding (Bmax) of platelet α 2 receptors, using 3H / I125, Yohimbine has been reported. However using agonists and antagonists, a state of hypersensitivity of α 2 receptors in depression has been put forward [7]. However, other evidence fail to support this suggestion There is far more consistency among studies of mononuclear cell-beta adrenergic receptors stimulated adenylate cyclase (AC) activity which find decreased responsiveness in depression. Attempts to assess the blunted GH response to clonidine in depression have yielded conflicting results.

Considerable evidence has occurred in the last two decades to support the hypothesis that alternation in 5-HT neuronal function in CNS occurs in depression [8]. Reduced CSF 5-HIAA, reduced 5-HT in post mortem brain of depressed and suicidal patients, decreased plasma tryptophan concentration and augmentation of 5-HT transmission following chronic treatment, clinical efficacy of 5-HT reuptake inhibitors and increased 5 H T2 binding sites in post mortem brain have been extensively studied. These studies support the hypothesis that alteration in 5-HT neural transmission play a major role in the pathophysiology of depression. Thus the measure of 5-HT receptor binding in platelets may provide a "window to the brain" and might provide a biochemical "marker" in monitoring response to pharmacotherapy.

GABA has also been shown to be involved in the development of depression and in the treatment of depression. The accumulated data reports that low plasma GABA level may present a biological marker of vulnerability for development of various mood disorders [9].

Lithium, an effective treatment for mania and the prevention of recurrent episodes, exerts multiple biochemical effects [10], [11]. Recently it has been shown that this monovalent cation acts as a potent uncompetitive inhibitor in the receptor coupled breakdown of inositol phospholipids, resulting in a relative depletion of inositol and an alteration in the generation of DAG [12]. Chronic administration of lithium markedly reduces a phosphoprotein, a substrate for protein kinase 'C' in rat brain [11].

Cholecystokinin (CCK) appears to play a role in stress responses in humans. Decreased levels of CCK in panic disorder have been reported. CCK antagonists appear to be potent anxiolytics. These agents have ability for blocking withdrawal from benzodiazepines or alcohol. These are non sedating and non dependent [13]. The CCK receptor antagonists like devazepide, lorglumide, L-365 and CL-988 have promised usage especially in benzodiazepine dependence. Among the different allosteric modulatory sites on GABA receptors, positive GABA receptor modulators along with benzodiazepine have been clinically exploited, like triazolam and alprazolam, full allosteric modulators; diazepam, a selective allosteric modulator and bretazenil the partial modulator. These, especially bretazenil and imidazenil, are expected to possess low tolerance and dependence liability.

Dementia is a disease characterized by general mental deterioration accompanied by disorientation, impaired memory, judgement and intellect. Alzheimer's disease (AD) is the commonest cause of dementia. Currently there is no cure and traditional treatment is directed at managing symptoms. However, there are avenues for development of new therapies which will hopefully be directed towards improvement of cognitive functions. Apart from the presence of neuritic plaques and neurofibrillary tangles, abnormalities in cholinergic system is linked to AD. Though biochemical abnormalities of cholinergic systems have been associated with degree of cognitive impairment, no alterations in post synaptic muscarinic cholinergic receptors in AD have been reported. Decreased acetylcholinesterase (AChE) in CSF and presence of antibodies against cholinergic components in blood and CSF of AD patients have been suggested as markers. Drugs like Tacrine which act by elevating ACh concentrations in cerebral cortex have been tried in AD. However drugs that prevent deposition of amyloid, that could restore the destroyed neuronal tissue and thus reverse the disease process and that act as antiviral agent would be the future directions in the treatment of AD. Nerve growth factor, obtained from fetuses, is one such agent that deserves special attention.

Currently, alcholism is the most important drug abuse problem world wide. There are no effective pharmacotherapies for alcoholism. The treatment of alcoholism is therefore of major social and medical interest. Increased knowledge about the neurobiology of drug reinforced behaviour and the basic molecular mechanism of alcohol dependence has paved the way for systemic exploration of receptor specific and selective pharmacological agents [14]. Various studies have shown that serotonergic drugs decrease alcohol drinking. SSRIs, like citalopram, decrease the number of drinking days. Recently acomprosate and naltrexone have been found promising in treating alcoholism.

Acomprosate, chemically known as calcium acetylhomotaurinate, is a CNS acting molecule and has the capacity to cross the blood brain barrier and is related to GABA, an inhibitory neurotransmitter. It primarily modulates GABA transport and also interferes with glutamate transmission at synaptic level. It also increases 5-HT levels in the synapse and has some opioid antagonist activity. Alcohol drinking has been shown to be influenced by alterations in opiate receptor activity. Opiate antagonists, such as nalaxone, may be safe and effective adjunct in the treatment of alcohol dependence. Methylsergide (5-HT1C antagonist) and LY 52857 (5-HT2 antagonist) failed to attenuate fluoxamine induced reduction

in ethanol intake. However, serotonin receptor agonists, including 8-OH-DPAT, buspirone, ipsaperone (5-HT1A agonists) and TFMPP (5-HT1B agonist) consistently decreased alcohol consumption in animal experiments. There is still a great need for drugs, in addition to alcohol deterrents, such as disulfiram, which could help in the management of alcoholism.

The supposition that multiple receptor subtype mediate the numerous physiological actions of 5-HT has recently been substantiated by molecular cloning. It is now clear that there are at least 15 distinct molecular entities of 5-HT receptors. Great progress has been made over the last decade in understanding the pharmacology of 5-HT, leading to the development of new drugs for treatment of several mental illnesses. Recent progress has centered around the discovery of multiple serotonin receptor subtype selective agonists and antagonists, as well as drugs that effect serotonergic system have great potential in treating depressions, OCD, anxiety and migraine [15]. Similar work is presently undertaken in the author's lab.

Commercial interest in finding ways to affect new 5-HT receptor subtypes continues to grow at rapid pace. In the recent years, a number of new and potentially atypical antipsychotic drugs have been developed on the basis of their high affinity at 5-HT2 receptors relative to D2 receptor [16]. Drugs such as serquel, resperidone, olanzapine, sertindole and zipa-rasidone fall in this category, whereas clozapine's atypical profile is due to its action on D2 receptor. The pharmacological basis for the difference between atypical and typical antipsychotics depends mainly on the ratio of 5-HT2A and D2 receptor affinity for these drugs. MDL100907, a potent and highly selective 5-HT2A receptor antagonist, without any D2 antagonist activity, is extremely potent as an atypical antipsychotic drug.

Studies have been focused on determining the involvement of specific 5-HT receptor subtype in the therapeutic action of antidepressant drugs. Antidepressants act by inhibiting 5-HT reuptake, thereby increasing the concentration of 5-HT and prolonging the temporary distribution of 5-HT. In this 5-HT1 receptor subtypes like 1A, 1B, 1D and 1E have been implicated in the action of antidepressants [17]. Similar work is in progress in our laboratory. The efficacy of specific antagonists and agonists of different subtypes of 5-HT receptors, which may be used as pharmacological agents is being studied in out lab.

Sumatriptan, a serotonin analogue, and dehydroergosine, an ergot derivative, both effective in migraine treatment, are 5-HT1A, 1B, 1D and 1F receptor agonists [18]. They block neurogenic inflammation in rat dura matter. The efficacy of 5-HT 1D agonist drugs in the acute treatment of migraine involves both central as well as peripheral 5-HT 1D receptors. Involvement of 5-HT 2B, a newest member of 5-HT2 family, in migraine has also been suggested. The novel distribution and functionality of 5-Ht 1A receptor has made ;this receptor a unique target for study in antidepressant action. Its role in the rapid clinical onset of antidepressant response produced by SSRI and pindolol combination is presently being evaluated.

The development of clomipramine and other serotonin re-uptake inhibitors has established a link between 5-HT and obsessive compulsive disorder (OCD). OCD is specifically responsive to drugs that affect serotonin, while drugs with nonserotonergic effects appear to be ineffective. Use of various agonists and antagonists specific to various 5-HT2 receptors subtypes has been studied with promising results. In spite of all the recent developments in techniques like molecular cloning, PET and NMR leading to understanding the molecular basis of mental illnesses, and to design and use of newer therapeutic agents for treatment, we are still far away from achieving full remission of the disease process. The future approach, if at all feasible in all cases, will be gene therapy.

Gene therapy and somatic cell therapy go hand-in-hand because of their close medical and scientific connections. Gene therapy involves deliberate alterations of the genetic material of living cell to diagnose, prevent or treat diseases. Nature of delivery system in gene therapy, as in any other therapy, is important. Use of vectors like suitably altered virus to render it innocuous to the host, monoclonal antibody or a cellular-receptor targeted ligant - DNA conjugate or DNA and liposome mixtures is the focus of recent studies. Here the expertise of genetic engineering is most sought after.

However, ethical, legal and moral issues apart from regulatory issues of gene therapy are of considerable interest recently. Only time and the efforts of interdisciplinary scientists will decide the future in the therapeutic management of mental illness which will lessen the burden both on patients suffering from such illnesses and on scientists, clinicians, administrators and family members who deal with such cases.

In this review, though an attempt has been made to include the recent developments in therapeutics in mental disease, I have been able to include only a few important mental disorders, where the newer strategies for therapeutic approach have been studied, is long.

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