EDITORIAL

Expanding the Neural Network and Utilizing Multi-Targeted Pharmacotherapy to Obtain Optimal Recovery for Complex Multi-Factorial Heterogenous Schizophrenia

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ABSTRACT

Schizophrenia is a complex heterogenous disabling disease that is a product of genetic and environmental factors. The patho-psycho-physiology of Schizophrenia is still not known completely. Manifestations of schizophrenia include positive, negative and cognitive symptoms. Pharmacotherapy mostly based on dopamine, glutamate and serotonin have not been successful in generating optimal recovery. Considerable gaps with unmet needs remain in Schizophrenia. Heterogenicity is the most likely cause of individual differences in symptoms of Schizophrenia in neurology and receptor pathways. The objective is to obtain optimal therapeutic success from multi-targeted pharmacotherapy. To achieve optimal therapeutic management, the following steps should be taken: a) treatment of early and prodromal concerns of schizophrenia should be treated early to stop continuation of neuropathological progression b) improve long-term therapeutic response c) avoid neurotoxicity caused by high drug dose use d) expand neural pathways (networks) to meet heterogenous and multifactorial needs of schizophrenia (in this paper seven such neural pathways are described) e) multi-targeted pharmacotherapy should be utilized to control all the neural pathways. Future research can hopefully produce the single target drug therapeutically capable to bind with all the neural pathways of schizophrenia syndrome.

INTRODUCTION

Schizophrenia is a complex heterogenous disabling disease that is a product of genetic and environmental factors. The patho-psycho-physiology of Schizophrenia is still not known completely. Manifestations of Schizophrenia include positive, negative and cognitive symptoms. Positive symptoms are comprised of auditory and visual hallucinations, delusions, abnormal thoughts and disorganized speech. Negative symptoms consist blunted affect, apathy, poverty of speech, anhedonia, loss of motivation and social withdrawal. Cognitive symptoms are: memory difficulties, concentration difficulties, and attention difficulties.

PRESENT PHARMACOTHERAPY

Pharmacotherapies have not been successful in bringing about complete recovery in spite of utilizing the present three expanded neural networks; which are dopamine, glutamate and serotonin. Drugs produced from these three neural networks have not completely fulfilled the expectation of full recovery of Schizophrenia. Thus, a considerable gap in treatment remains and also unmet needs for recovery are not met. Furthermore, the glutamate neural network drugs seem to have difficulty exerting clinical efficacy solely in Schizophrenia[1-3,16)]. Thus, expanding the neural network more than above three neural networks, will significantly meet unmet needs, through pharmacotherapy; and optimal recovery will also occur. Heterogenicity is also important to take into account for obtaining optimal therapeutic success in Schizophrenia. Schizophrenia patients have marked variations in symptoms in biological and clinical domains, and in receptor pathways. Heterogenicity is most likely the cause of individual differences in Schizophrenia symptoms in conjunction with underlying neurobiological changes and receptor pathways. In reality, Schizophrenia is a syndrome which is based on a combination of various types of sub-groups and different symptoms. To obtain optimal benefit from treatment, it is important that future steps should recognize various molecular pathways including neurodevelopmental modalities and synaptic integrity. Other important factors that contribute to an incomplete and unsatisfactory response to present-day treatment in Schizophrenia are: 1) Prodromal and early Schizophrenia treatment are delayed. Neuropathological progression continues and causes detrimental effects 2)Delaying early treatment may also worsen the long-term therapeutic response of treatment 3) On the other hand, long-term effects of antipsychotics can be neurotoxic 4) Higher doses of antipsychotics may also produce long-term poor prognosis, while acute phase treatment, utilizing maintenance treatment, will be more beneficial to Schizophrenic patients and, 5) The need to expand neural pathways (networks) for multi-targeted drugs for the treatment of complex heterogenic and multi-factorial of Schizophrenia syndrome, as this will bring the best possible therapeutic results[1-4)].

FUTURE PHARMACOTHERAPY

Pharmacotherapies for therapeutic success should be achieved by multi-targeted ligand, based on multi-targeted drug design. Expansion of more than three neural pathways should include the following suggestions[1-4,16)] : 1) GABA (gamma-aminobutyric acid) pathway, 2) TAARI (trace-amine associated pathways), 3) microbiome brain axis root, 4) muscarinic, nicotine acetylcholine pathways, 5) neuroinflammations and stress inflammations pathway, 6) genetic risk and its therapeutic role,

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and 7) epigenetic pathways.

1. GABA (gamma-aminobutyric acid): This is a major inhibitory neurotransmitter and is central to brain rhythm-generating network and synchrony of neural oscillation network[4,5]. GABA initiates affect, working memory, consciousness, and perception. In Schizophrenia memory impairment is caused by this network[4-8].

In clinical studies, GABA Agonists have shown to be effective in improving core Schizophrenia symptoms[4-8]. The changes by GABA occur in both presynaptic and postsynaptic components[9]. The dysregulation of excitatory and inhibitory balance is lost and GABA interneurons do not work properly. GABA drugs' function is primary through neuropathological mechanism responsible for cognitive symptom changes in Schizophrenia patients[10,11]. Post mortem and animal studies have shown that GABAergic drugs selectively modulate and cause improvement in episodic working memory and executive function. However, the mechanism of interaction of GABA with other neurotransmitter needs to be further studied for knowing the full therapeutic role of GABA in pharmacotherapy of Schizophrenia. Molecular underpinnings of excitatory and inhibitory balances should be further researched to improve etiological understanding, and also to uncover new targets for future drug discoveries[12-16].

2. TAAR1 (trace amine associated receptor 1) is a member of TAAR family and is G protein coupled receptor mostly expressed in ventral tegmental area (VTA) and dorsal raphe nucleus (DRN) including prefrontal cortex and nucleus accumbens. TAAR1 is structurally related to monoaminergic neurotransmitter and modulates presynaptic dopamine synthesis capacity which maybe responsible for producing antipsychotic-like effect[17-24]. TAAR1 also interacts by activating 5-HT1A receptors while modulating serotonergic signalling by inhibiting D2[21,24]. Modulatory functions on dopaminergic and serotonergic receptors have made TAAR1 an important and interesting target for pharmacological intervention. TAAR1 has agonist activities and shows the antipsychotic properties for the treatment of psychosis and negative symptoms without producing significant neurological and metabolic adverse reactions. SEP363856 is one important example of a drug developed by this avenue. This drug has shown significant therapeutic effect on psychosis and negative symptoms with mild neurological and metabolic effect[23,24].

3. Microbiome brain axis model: This model has been increasing in focus for etiology and therapeutic process of Schizophrenia[25-28]. This model is based on bidirectional communication between the central and enteric nervous system and ensures the connection of brain with peripheral intestinal system. The gut microbiome plays a significant critical role in brain development by programming the brain function during early development. Epigenetic mechanism[29,32,76] is the pathway for gut microbiome to affect brain development. Signal pathway from gut microbiome to brain includes numerous mechanisms but main pathways are as follows: a) immune system which neurophysiologically work through cytokine' effect, b) through activation of vagus nerve and, c) protection of various metabolism which cross to blood brain barriers (BBB) to regulate neurological functions. Through these pathways of microbiota brain axis communication controls central physiological processes such as neurogenesis, neuroinflammation and neurotransmission[29-31,33]. Probiotics modulate the immune response of persons suffering from Schizophrenia and could be beneficial to Schizophrenia disorder[31,33-39]. Gut brain communication supports the secretion of some neurotropic substances and some intestinal bacteria which can produce mediators like GABA and acetylcholine[33,38-40]. The research and their generated reports show that lactobacillus and bifido bacterium administered to chronic Schizophrenia patients as an adjunct treatment increases the level of brain derived neurotrophic factors[40-42].

4. Muscarine cholinergic receptors (agonist peripheral M1, M4 and antagonist M5): Muscarinic acetylcholine receptor subtypes can modulate specific brain circuits and thus bring out improvements in positive, negative, and cognitive symptoms[44]. Strong support for muscarinic cholinergic role in Schizophrenia comes from post mortem and brain imaging studies[55]. Muscarinic and nicotinic acetylcholine pathways have become the focus of developing antipsychotic drugs[43,45-52]. The combination of Xanomeline and Trospium chloride[49,53] have produced significant antipsychotic efficacy with improved safety profile in Phase II study. Xanomeline, an mAchR/M4 preferring agonist alone was utilized in refractory Schizophrenia and caused procholinergic side effects like nausea, diarrhea and vomiting. However, the combination with Trospium chloride the adverse effects of procholinergic type were eliminated and safety profile of combined medication (Xanomeline and Trospium) significantly improved[49,54]. One of the proposed mechanism of activity indicates that the combined drugs reduces the cholinergic tone within striatum thus reducing striatal dopamine level. The involvement of Xanomeline is in pathophysiology of Schizophrenia and has no direct effect on dopamine. Pharmacologically, Xanomeline is selective M1 and M4 receptor agonist whereas Trospium is a pan muscarinic antagonist; and the combination of both brings out the best of Xanomeline by eliminating the adverse reactions. In spite of good therapeutic results of combined drugs, larger and longer duration studies are needed for finding the best flexible ratio of combination confirming the best therapeutic efficacy.

5. Neuroinflammation Immune System Dysregulation and Stress Model: Neuroinflammation model of Schizophrenia in the light of recent research has been enlarged to Vulnerability Stress Inflammation Model[55-60,67]. There have been the following findings which confirm validity and recognition of this model: a) stress usually increase proinflammatory cytokines along with acute phase protein and contributes to neuroinflammation. Immune inflammatory disturbance in Schizophrenia show that IL-6 is one of the most commonly distributed cytokines besides others like IL-1, TNF and IFN[58-60], b) low level neuroinflammation are observed in neurotransmission of Schizophrenia with dysregulation of immune system, c)antipsychotics usually provide anti-inflammatory and immunomodulatory effect[58-63], d) prenatal inflammatory events seen as infection, environmental stresses and alteration in immune system lead to synaptic plasticity disturbance. This plasticity disturbance plays and important part in neuroinflammation and causes disturbed neurodevelopment in the fetus. Developmental disruption in early brain development can cause heightened vulnerability to stress. Stress also leads transition to psychosis which increases the inflammatory markers.

Stress in vulnerable individuals can also lead to first episode psychosis and also relapses in Schizophrenia. Anti-inflammatory agents have been tried in the treatment of Schizophrenia[61] and have been shown therapeutic responses and efficacy; but the therapeutic responses and benefit has not been convincing[61]. The possible interplay of immune activated microglia and cytokines can be involved through inflammatory process in the course of Schizophrenia. This can provide some scientific basis for role of therapeutic efficacy as an adjunct to antipsychotic medication for the treatment of Schizophrenia[60,61,65-67].

6. Genetic Risk and its Therapeutic Role: The neurobiology involved in the genetic risk of Schizophrenia is complex. Over one hundred small nucleotide polymorphisms copy many variations and changes in gene expression; making the understanding that the genetic risk and their suitability for therapeutic gain are very difficult to find. Schizophrenia represents multidimensional complex phenotypes. GWAS have revealed large number of alleles and more than one hundred loci many of which contain multiple genes and polygenic scores allows us to determine risk of Schizophrenia with minor susceptibility. Large number of alleles indicate the Schizophrenia risk through polygenic route[74]. The concept of monogenic disorder for Schizophrenia has been therefore abandoned a long time ago, while gene expression confirms polygenic risk[67-75].

7. Role of Epigenesis in Schizophrenia in Etiology and Therapeutic Goal: Schizophrenia has impact from environmental factors and genetic factors and both play an important part in the pathogenesis of Schizophrenia. Epigenetic changes in Schizophrenia thus represent mixed factors and can reveal etiological window, provide help in therapeutic management, and prevention of heterogeneous Schizophrenia disorder. Phenotype expression of Schizophrenia is mainly due to complex interactions between risk alleles and environmental risk factors[76] in response to positive and negative environmental stimuli[76]. Epigenetic alteration at the reelin promoter plays important part in epigenetic process. Histone post transcriptional modification, regulation of chromatin structure, microRNA regulation of signalling pathways including those involved in DNA methylation are main pathways of Schizophrenia[76-80].

These signalling pathways with the involvement of DNA methylation are a dynamic process which are capable to meet the need of environmental stimulus with polygenic gene factors. Epigenetic abnormalities including faulty communication in between various epigenetic mediators as described in pathways are significant cause of Schizophrenia disorder. Epigenetic mechanisms also regulate gene function and cause change in nucleotide sequences of DNA in Schizophrenia. Abnormal epigenetic liabilities to Schizophrenia are able to superimpose on polygenic risk through various pathways described above.

DISCUSSION

Unmet needs, and a minority of Schizophrenia patients not responding to present treatment are a common phenomenon. With drugs available at present, the therapeutic responses has been unsatisfactory. The

reasons for such an unsatisfactory response are many; but the important scientific reasons are as follows:

a) Schizophrenia patients are heterogeneous and exhibit marked variation in symptoms, and the biological characteristics of symptoms are not clear. The three neural pathways (dopamine, glutamate and serotonin) are successful in controlling psychotic symptoms produced mostly by the three neural pathways; but other symptoms produced by other pathways are not controlled by present treatment. These pathways should be controlled by multi-targeted drugs or drugs which bind to uncovered pathways b) difficulties in recognizing early and prodromal phases; and seldom are these phases treated. This allows progression of neuropathological causes of Schizophrenia and poses difficulty in treating at the advanced stage. The delay of the treatment delays the satisfactory response of treatment. The present recommendation should be followed by starting comprehensive treatment as early as possible and avoid relapse while minimizing the adverse reaction of treatment c) Long-term treatment also remains a problem in itself. Questions have been raised that long-term treatment may cause neurotoxicity. Reduced brain volume and long-term use of drugs may also cause neurotoxicity d) high dose of medications use is also not very therapeutic as high dose of medications also precipitate neurotoxicity. Developing maintenance treatment and drug discontinuation should be tried with a view to controlling the relapse if it occurs by treatment. Twenty percent of patients treated in the early phase of Schizophrenia go into remission and do not need further treatment.

Comprehensive pharmacotherapy to cover all neural paths encompasses two scenarios: the first is that single drug of future has the capacity to bind multiple targets; the second scenario is to utilize multiple drugs to bind multiple targets. Polypharmacy as described in the second scenario is defined as use of drugs to act on multiple targets of disease pathways. In 2014, National Library provided scientists with the above definition but also suggested that drug interaction risk should be avoided or controlled. Combining multiple drugs binding to multiple targets has now become an acceptable therapeutic way to be used in various diseases.

In recent years development of a single molecule with multi-target drugs (MTDS) has become increasingly feasible. However, it still remains a difficult, complex and challenging situation.

CONCLUSION

Schizophrenia is a multi-targeted, complex and heterogenous syndrome and needs pharmacotherapy with multi-targeted drugs. This is challenging; but with future research and new techniques, it is feasible. This paper has suggested the uncovered pathways to be treated by pharmacotherapy for the optimal treatment of Schizophrenia as a syndrome. Future goals should be to design either single drug with multiple bindings or multiple drugs to bind with all the multiple targets of Schizophrenia. Structure-based virtual scenarios for potential antipsychotics with multi-targeted designs have been produced[81,82,83]. Future research will bring knowledge-based approaches, screening approaches and computational approaches, alone or in combination, to find single or multiple drugs for the treatment of Schizophrenia syndrome.

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