Benzisoxazole derivatives as Atypical Antipsychotic drugs: A Review

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Antipsychotic medications constitute a diverse series of heterocyclic compounds that are used to treat psychotic problems, particularly schizophrenia and bipolar affective disorders. Heterocyclic molecules such as benzisoxazole derivatives, especially 3-(piperidin-4-yl)-1,2-benzisoxazole have been widely used as antipsychotic drugs. Atypical antipsychotic drugs which are derived from benzisoxazole include risperidone, iloperidone and paliperidone.

Their therapeutic mechanism is to act as potent antagonists to D_2 dopamine receptors and blocks 5-HT$_{2A}$ receptors. However, the administration of antipsychotic drugs is accompanied with propensity to cause extrapyramidal symptoms (EPS) such as psuedoparkinsonism, tardive dyskinesia, acute dystonic reactions and akathisia. Risperidone, paliperidone and iloperidone exhibit better efficacy compared to other known antipsychotic drugs, based on their mechanism in the dopaminergic and serotonergic systems. However other antipsychotic drugs have exhibited lesser propensity to cause EPS than the benzisoxazole derived drugs. Thus reconsideration of structure-function relationship of 3-(piperidin-4-yl)-1,2-benzisoxazole derived drugs and designing new molecules with changes in the structure that support lower propensity to cause EPS may serve a long drawn objective to design antipsychotic drugs with higher efficacy and lesser EPS.

Risperidone, paliperidone and iloperidone categorized as atypical antipsychotic drugs [1] have principal action in humans, namely the repression of schizophrenia and bipolar affective disorders. The above drugs are classified as second generation atypical antipsychotics whose elementary mechanism of action is seen as D2/5HT2A antagonism with higher affinity towards 5HT2A [2]. Their ability to cause extrapyramidal side effects (EPS) in humans and catalepsy in mice has made them to be designated as neuroleptics [3]. They are known to block dopamine D2 receptors in the mesolimbic region, particularly stria terminalis, nucleus accumbens and the amygdale [4-6]. The drugs not only show affinity for D2/5HT2A but also for other cholinergic, histaminergic, 5-HT1A, α1-adrenoceptors systems thus designated as multi-acting receptor-targeted antipsychotics (MARTA) [7]. However the above mentioned atypical antipsychotics have been known to be more effective and safer than the conventional antipsychotics [8]. Earlier studies have exhibited comparable results in control of positive symptoms by both conventional and atypical antipsychotics and pre-eminence of atypical antipsychotics over conventional drugs in the control of negative symptoms and cognitive dysfunction [9]. Efficacy of atypical antipsychotics also include better functional capacity, increased quality of life, efficiency in patients with refractory problems and higher rate of response [10]. Nevertheless atypical antipsychotics exhibit characteristic side effects, their cognitive and metabolic side effects are of particular interest [11]. However, atypical antipsychotics according to earlier studies have been the first choice of medication in schizophrenia and bipolar disorders [12, 13], with iloperidone exhibiting better efficacy than other antipsychotics [14].

Interestingly few studies have revealed that atypical antipsychotics though considerably more efficacious than conventional antipsychotics but show equal propensity to cause extrapyramidal side effects [15]. However authors have found that benzisoxazole derivative antipsychotic drug risperidone were remarkably more efficacious than the conventional drugs, also showing better functional recovery. Risperidone were also found to be better than conventional antipsychotics with regard to positive symptoms and optimally higher with respect to negative symptoms and cognitive problems. The discussion reveal the heterogeneity in the function of benzisoxazole derived antipsychotics, however few studies also revealed superiority of these drugs as antipsychotics with same EPS rate as that of placebo [16, 17].

Mechanism of action of antipsychotics

The supposed mechanism of action of benzisoxazole derived atypical antipsychotics is classified into serotonergic, dopaminergic and combined regulatory effects. Since the above antipsychotics mainly exhibit antagonism to D2/5HT2A/H1/α adrenergic systems, the overview of discussion will focus comprehensively on these systems.

Dopaminergic regulation

Dopamine a neurotransmitter acts by means of two groups of receptors. "D1 like receptors" mainly D1 and D5 receptors, function by increasing cAMP levels. "D2 like receptors" D2, D3 and D4 receptors function by decreasing cAMP levels [18-20]. Blocking of D2 receptor is a general pharmacodynamic action of all atypical antipsychotics resulting in exhibiting potential antipsychotic properties [21].All benzisoxazole derived antipsychotics iloperidone, risperidone and paliperidone are known to block D2 receptors [22-24]. The percentage affinity and level of dissociation of these atypical antipsychotic drugs from the receptors determine the rate of EPS caused [25, 26]. It has been proved that occupancy of D2 receptor >80% in most of the cases are associated with EPS [27-32]. A lesser D2 receptor affinity complemented by lower D2 receptor occupancy by the above mentioned atypical antipsychotic drugs have rendered them the antipsychotic properties. Iloperidone has also shown lower affinity for D1 receptors [33]. D_1 receptors are the main dopamine receptors in the prefrontal cortex, and antagonism to these receptors is known to exhibit therapeutic effects on negative [34] and cognitive effects of schizophrenia [35]. D_2 receptors are known to interact with D_1 receptors at the cellular level, thus D_1 antagonism may affect cognitive disorders at the D_2 receptor modulation [36, 37].

Rapid dissociation of iloperidone, risperidone and paliperidone form D_2 receptors is one of the reasons for better EPS report of the atypical antipsychotics, supported by the fact that it has lesser affinity for D_2 receptors. The occupancy levels of the D_2 receptors by the neurotransmitter dopamine are found to be 25-40% [38] and the atypical antipsychotics compete with dopamine to bind to D_2 receptors. The antipsychotic drugs which exhibit faster dissociation (K_{off}) form the receptor are said reach early equilibrium between association and K_{off} in the course of action of receptor binding along with constant binding and release of endogenous dopamine. In equilibrium state, atypical drugs like Iloperidone and risperidone can bind and dissociate faster than the conventional drugs, thus assuming more effective properties in interfering with dopamine binding to D_2 receptors [26]. Blockade of D_4 receptors is also a probable mechanism of benzisoxazole derived atypical antipsychotics in treating bipolar affecting disorders and schizophrenia. Atypical antipsychotics exhibit increased affinity towards D_4 receptors compared to D_2 like receptors, whereas, first generation antipsychotic drugs have exhibited more or less, similar affinity for D_2 and D_4 receptors. This was further supported by rate of catalepsy induction (model of EPS studies) in laboratory animals, which showed decrease in catalepsy in relation to higher D_4 receptor affinity towards atypical antipsychotics [39]. The higher levels of dopamine in the prefrontal cortex and basal ganglia induced by antagonistic property of the atypical antipsychotic drugs towards D_4 receptors suggests the lower rate of EPS and therapeutic effects on cognitive symptoms [40]. Interestingly drugs showing affinity towards only D_4 receptors have failed to exhibit therapeutic potentials [41]. This suggests that D_4 receptor antagonism is only effective when acting as a complementary to blockade of D_2 receptors.

Serotonergic regulation

Historical findings that indicated the role of $5HT_{2A}$ receptor came from the $5HT_{2A}$ receptor agonists Lysergic acid diethylamide (LSD), which is a strong psychedelic drug that alleviate psychotic problems [42]. Blockade of $5HT_{2A}$ receptors by LSD has suggested a strong mechanism of treating cognitive disorders like schizophrenia. $5HT_{2A}$ receptors are localised in hippocampal and cortical pyramidal cells which is gives a strong evidence of involvement of serotonin receptors in antipsychotic effects. However highest density of $5HT_{2A}$ at the fifth neocortex layer which is region main of neurotransmission [43, 44]. $5HT_{2A}$ receptor antagonism leads to depolarisation of pyramidal cells, thus leading to normalisation of pyramidal cell activity. The above hypothesis is the reason for antipsychotic potentials of benzisoxazole derived antipsychotics [45]. $5HT_{2A}$ receptor localisation on dopaminergic neurons in substantia nigra and ventra tegmentum including their terminals are related to their combined effect with D2 system [46] and $5HT_{2A}$ antagonism at this regionis known to modulate the activity of dopamine neurons [47]. $5HT_{2A}$ regulates the activity of the striato-pallidal GABA neurons [48], thus antagonism of $5HT_{2A}$ receptors at pallidal GABA cells would counter the inhibition of neurotransmission. This may explain the lowered risk of EPS when administered with atypical antipsychotics, which is also supported the fact that SSRI`s may also cause EPS [49].

Combined regulation of $5HT_{2A}$ and D_2 receptors

Blockage of D_2 and $5HT_{2A}$ receptors is the principle difference between benzisoxazole derived atypical antipsychotics and conventional antipsychotic drugs [50, 51]. According to nigrostriatal dopaminergic pathway, the blockade of $5HT2_A$ receptors leads to rise in entry of dopaminergic neurons into the striatum. This amplified activity of dopamine in the striatum displaces the antipsychotic drug from the D_2 receptors and thus decreases the propensity to cause EPS [52]. Optimum efficacy of resperidone, iloperidone and paliperidone against the positive symptoms of cognitive disorders is associated with 5-HT_{2A}/D_2 receptor antagonism on the mesolimbic dopaminergic pathway into the nucleus accumbens. In the above process, 5-HT_{2A} receptor agonists led to higher dopaminergic output [53], despite the fact that antagonists decreased dopaminergic output [54]. Serotonergic effects of benzisoxazole derived atypical antipsychotics are also found to be seen in blockade of $5HT_{2C}$ and D_2 receptors [55]. 5HT2c receptors are known to regulate the inhibition of dopaminergic production by means of

serotonin from the antagonism towards ventral tegmentum, the effects were found to be similar to that of $5HT_{2A}$ receptor blockades [56, 57]. The increase in the levels of dopamine in nucleus accumbens and prefrontal cortex suggests the fact that $5HT_{2C}$ and $5HT_{2A}$ receptor blockade together is more efficient than blockade of 5 HT_{2A} receptors [58].

5 HT2A/D2 hypotheses theoretically also comply with agonism of 5HT1A and D2 receptors blockade. 5 HT2A and 5 HT1A receptors moderately exhibit contradictory functional effects [55]. Therefore similar to 5HT2A receptor antagonists, 5HT1A receptor agonists play a prominent role in increase of dopamine levels in the striatum and neocorticular region [59]. The concentration of 5 HT1A receptors in the pre and postsynaptic regions also play a significant role [60].

α-Adrenergic and D2 receptor regulation

Benzisoxazole derived atypical antipsychotics exhibit relatively moderate affinity for α adrenergic receptors. Earlier studies regarding α adrenergic receptor antagonism is given by prazosin (a α adrenergic receptor antagonist) administered along with haloperidol decreased the possibility of EPS and lead to increased binding of the drug to limbic Dopamine D2 receptors [61, 62]. This observance is supported by the blockade of α adrenergic receptor leading to inhibition of 5HT receptors in the raphe nuclei resulting in similar effect to that of 5-serotonin receptor blockade by 5-HT2/ D2 receptor antagonist [63]. Benzisoxazole derived atypical antipsychotics have very low affinity for muscarinic [M1-M4] receptors and binding to their receptors is not essential for their therapeutic action [64].

CONCLUSION

Benzisoxazole derived atypical antipsychotics such as iloperidone, risperidone and paliperidone have invariably exhibited their antipsychotic potential by blockade of dopamine D2 receptors in the mesolimbic region, which indicates increased dopaminergic activity. These atypical antipsychotics have also shown block serotonin receptors particularly 5HT2A receptors, however these drugs also are known to potentiate 5HT1A mediated effects on dopaminergic neurons in the mesostriatal, mesolimbic and mesocorticular regions. However the based on the affinity to D2/5HT2A receptors and their dissociation have reflected in the occurrence of EPS. So, atypical antipsychotic drugs if designed such that moderate affinity to these receptors and early dissociation may serve a long drawn objective of antipsychotic drugs high efficacy and lower risk of EPS.

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