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DOPAMINE TARGETING DRUGS FOR THE TREATMENT OF SCHIZOPHRENIA: CURRENT TREATMENT, DEVELOPMENT OF ANTIPSYCHOTICS, COMPARISON OF ANTIPSYCHOTICS

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ABSTRACT

Schizophrenia is a chronic and debilitating neuropsychiatric disorder affecting approximately 1% of the world's population. This disease is associated with considerable morbidity, placing a major financial burden on society. Antipsychotics have been the mainstay of the pharmacological treatment of schizophrenia for decades. The traditional, typical and atypical antipsychotics demonstrate clinical efficacy in treating positive symptoms, such as hallucinations and delusions, while they are largely ineffective and may worsen negative symptoms, such as blunted affect and social withdrawal, as well as cognitive function. The inability to treat these latter symptoms may contribute to social function impairment associated with schizophrenia. The dysfunction of multiple neurotransmitter systems in schizophrenia suggests that drugs selectively targeting one neurotransmission pathway are unlikely to meet all the therapeutic needs of this heterogeneous disorder. However, unintended engagement of multiple pharmacological targets, or excessive engagement of intended targets, can lead to adverse effects and poor tolerability. In this article, we will review marketed typical and atypical antipsychotics and new therapeutic agents targeting dopamine receptors and other neurotransmitters for the treatment of schizophrenia. Representative typical and atypical antipsychotic drugs, as well as new investigational drug candidates, will be systematically reviewed and compared with respect to structure-activity relationships, pharmacokinetic properties, drug metabolism and safety, pharmacological properties, preclinical data in animal models, clinical outcomes, and

associated side effects.

KEYWORDS: Antipsychotic, Aripiprazole, Clozapine, Dopamine, Haloperidol, ITI-007, Risperidone, Schizophrenia.

1. INTRODUCTION

1.1. Schizophrenia

Schizophrenia is a chronic neuropsychiatric illness affecting approximately 1% of the global population. Individuals with the disorder may experience hallucinations, delusions, suspiciousness, and conceptual disorganisation, among other so-called positive symptoms. These positive symptoms can be accompanied by social withdrawal, blunted affect, emotional withdrawal and asociality, collectively referred to as negative symptoms. Cognitive impairment is also a core feature of schizophrenia. Together with other residual symptoms, including depression, the broad array of symptoms associated with schizophrenia results in significant impairment of social function, with the inability to fully integrate into one's family and into the workplace. Although the aetiology and pathology of schizophrenia remain largely unresolved, dopamine system dysfunction clearly contributes to the pathophysiology of this disorder. Subsequent research suggests that the serotonergic pathway also plays an important role. Recent molecular genetic studies conducted by an international schizophrenia consortium strongly support the fact that schizophrenia is a polygenic disease.

1.2. Current Treatments for Schizophrenia

It is well accepted that the positive symptoms of schizophrenia are associated with hyperdopaminergic neurotransmission in the brain, particularly in the mesolimbic dopamine pathway, while the negative symptoms and cognitive deficits associated with schizophrenia may be caused by hypodopaminergic activity in the mesocortical pathway. Dopamine D2 receptor antagonists, such as chlorpromazine and haloperidol, have demonstrated clinical efficacy in the reduction of positive symptoms. However, these first-generation antipsychotics are ineffective and may exacerbate negative symptoms and cognitive deficits associated with schizophrenia. As detailed below, they bind to a number of receptor systems, many of which contribute to serious side effects. Although modulating dopamine neurotransmission has been a dominant therapeutic approach, findings from both clinical and preclinical research have suggested that dysregulation of other neurotransmitter systems, including serotonin, glutamate, gamma-aminobutyric acid (GABA) and acetylcholine, also contribute to the pathophysiology of schizophrenia. The dysfunction of multiple

neurotransmitter systems in schizophrenia indicates that drugs selectively targeting one neurotransmission pathway are unlikely to meet the therapeutic needs of this heterogeneous disorder. Treatment involving the modulation of multiple targets may be more effective in addressing social dysfunction as well as positive symptoms associated with schizophrenia. In this article, we will review marketed typical and atypical antipsychotics as well as novel therapeutic agents targeting dopamine D2 receptors and other neurotransmitter systems for the treatment of schizophrenia. The structure-activity relationships (SAR) and receptor binding profiles of these compounds will be discussed. Representative compounds from each generation of antipsychotics will be compared in various aspects, including pharmacological profiles, efficacy in behavioural models, clinical outcomes and associated side effects.

2. DEVELOPMENT OF ANTIPSYCHOTICS FOR THE TREATMENT OF SCHIZOPHRENIA

Since the first antipsychotic, chlorpromazine, was introduced in the 1950s, many other antipsychotic drugs have been discovered and marketed during the past six decades. While the chemical structures of these antipsychotics are quite diverse, they all have somewhat similar pharmacological action, mainly dopamine D2 receptor blockade. These compounds generally can be classified as “typical” and “atypical” antipsychotics based upon both the pattern of clinical effects and mechanism of action. The typical antipsychotic drugs, represented by haloperidol and chlorpromazine, are also called the first-generation antipsychotics (FGA) or neuroleptics. The FGAs are effective at reducing positive symptoms associated with schizophrenia, but are largely limited by extrapyramidal motor side effects (EPS), hyperprolactinemia and cognitive dulling. These adverse effects are likely mediated by high dopamine D2 receptor occupancy. The serendipitous discovery of compounds such as clozapine defined a new generation of antipsychotic medications, referred to as the atypical antipsychotics. The atypical antipsychotics, including clozapine and risperidone, are considered the second-generation antipsychotics (SGA). Serotonin 5-HT2A receptor antagonism in combination with D2 receptor antagonism is thought to be the hallmark pharmacology of the SGAs. The SGAs have reduced EPS liability compared to the FGAs, but can be associated with increased weight gain and metabolic burden mediated by unintended off-target pharmacological interactions. Many are still associated with high rates of akathisia, even though rates of Parkinsonism have been reduced in some compounds. Clozapine, arguably the most effective antipsychotic, has a myriad of safety issues that preclude it from being used as a first-line therapy. The more recently marketed antipsychotics with D2

receptor partial agonist effects rather than D2 antagonism, as exemplified by aripiprazole and brexpiprazole, are still considered as atypical antipsychotics, though these drugs were marketed as the third generation antipsychotics. Presynaptic partial agonism at D2 receptors has allowed for a further reduction in EPS and hyperprolactinemia, but postsynaptic partial agonism at D2 receptors has been associated with relatively high levels of akathisia and, more recently, with uncontrollable pathological urges to gamble, binge eat, shop and have sex. Currently, new investigational drugs with novel mechanisms are being developed to identify better therapeutic agents that can treat not only the positive symptoms of schizophrenia but also enhance social function and improve safety and tolerability. For instance, ITI-007 represents a first-in-class small molecule therapeutic agent interacting with serotonergic, dopaminergic and glutamatergic neurotransmitter targets in a complex, unique and regionally selective manner. We will briefly review the first and second generation antipsychotics since these antipsychotics have been reviewed extensively. Newer antipsychotic drug candidates targeting dopamine, along with other neurotransmitter systems, will be discussed in detail. Representative antipsychotic drugs, haloperidol, clozapine, risperidone, aripiprazole, and ITI-007, representing a new investigational drug for schizophrenia, will be systematically reviewed.

2.1. Haloperidol and Other First-Generation Antipsychotics (FGA)

Typical antipsychotics exert their action predominantly through dopamine D2 receptor antagonism. As exemplified in these first-generation antipsychotics, they may be generally categorised into several chemical classes, including phenothiazines, such as chlorpromazine, perphenazine, fluphenazine, trifluoperazine and levomepromazine, thioxanthenes, such as chlorprothixene, clopenthixol and thiothixene, and diphenylbutylpiperidines, such as pimozide, fluspirilene and penfluridol.

Representative first-generation antipsychotics from the phenothiazine, thioxanthene and diphenylbutylpiperidine series.

Butyrophenones are another important class of compounds with antipsychotic activities. Haloperidol is a well-known typical antipsychotic drug that belongs to this chemical class. Other drugs, such as bromperidol, trifluperidol, lenperone, benperidol, droperidol, pipamperone and spiperone are also from this family. These butyrophenones have different receptor binding profiles. Each of these compounds exhibited different clinical efficacy. For instance, bromperidol possesses a dopamine D2 receptor binding affinity similar to that of

haloperidol, yet it has an apparent elimination half-life of approximately 24 h, supporting a once-daily dose regimen. Trifluperidol is a more potent neuroleptic drug than haloperidol and has been studied in withdrawn and autistic patients with schizophrenia. Benperidol and spiperone are two of the most potent antipsychotic drugs in the butyrophenone family, though not approved for use in the United States. Spiperone has shown efficacy in treating drug-resistant schizophrenia. Droperidol is a short-acting neuroleptic drug with pronounced antiemetic and anti-shock properties, though it is not used for the treatment of schizophrenia due to its short duration of action. Pipamperone is generally classified as a representative first-generation antipsychotic from the butyrophenone chemical class.

Among these typical antipsychotics, haloperidol is the most commonly used, so its properties will be extensively reviewed in this article and compared with representative examples of newer generations of antipsychotics. Haloperidol was first synthesised by Bert Hermans at the Janssen Laboratories in Belgium in February, 1958. It was given the generic name of haloperidol because of the two halogenated substituents incorporated into the molecule. Under the brand name Haldol®, haloperidol was marketed in Belgium in 1959 and later marketed in the United States and other countries. It is currently on the World Health Organisation (WHO) Model List of Essential Medicines. This compound preferentially binds to dopamine and α1-adrenergic receptors with negligible affinity for serotonin 5-HT2C, histamine H1 and muscarinic M1 receptors, which are thought to be associated with adverse effects of marketed antipsychotics.

Haloperidol is extensively metabolised in the liver. In humans, the compound primarily undergoes glucuronidation, ketone reduction to stereoselectively generate the (S)-enantiomer of reduced haloperidol via a ketone reductase, and N-dealkylation to give dealkylated metabolites via cytochrome P450 3A4 and 2D6. The reduced haloperidol can also be back converted to haloperidol via CYP 3A4, as shown in. It has been suggested that haloperidol is also subjected to cytochrome P450-mediated metabolism to form pyridinium metabolites, structural analogues of MPP+ (1-methyl-4-phenylpyridinium). In psychiatric patients treated with haloperidol chronically, the severity of tardive dyskinesia and Parkinsonism appears to be associated with an increased ratio of pyridinium to haloperidol. To prevent the formation of pyridinium metabolites, a new chemical series of antipsychotic agents was designed based on the primary metabolic pathways of haloperidol. The glucuronidation of haloperidol catalysed by uridine 5'-diphospho-glucuronosyltransferase (UGT), the haloperidol scaffold

has been reported in recent years.

2.2. Clozapine, Risperidone, Aripiprazole and other Second-Generation Antipsychotics (SGA)

Unlike the typical antipsychotics, which preferentially block dopamine D2 receptors, the second-generation antipsychotic drugs not only reduce dopamine neurotransmission but also act on serotonin receptors, especially 5-HT2A receptors and typically as antagonists. Biochemical, electrophysiological and behavioural studies have shown that 5-HT2A receptor antagonists have antipsychotic-like activity. The highly selective 5-HT2A antagonist, MDL-100907, exhibited antipsychotic activity in several preclinical animal models, but it failed, like other selective 5-HT2A antagonists, to exhibit sufficient efficacy in clinical trials to be approved for the treatment of schizophrenia. To achieve better efficacy, blockade of both serotonin 5-HT2A and dopamine D2 receptors is warranted at clinically effective doses. There is now considerable preclinical and some clinical evidence that effects on 5-HT receptors contribute to the low risk of producing EPS, which is the defining characteristic of the atypical antipsychotics, compared to typical antipsychotics.

Importantly, the data suggest that 5-HT2A receptor antagonism potentiates mesolimbic D2 receptor antagonist-mediated efficacy, but does not alter nigrostriatal D2 receptor antagonist-mediated motor side effects. Ritanserin, a 5-HT2A/C receptor antagonist, enhanced raclopride-induced dopamine concentrations in the medial prefrontal cortex and raclopride-induced increases in accumbal dopamine signal, but not in the striatum. Ritanserin potentiated raclopride's antipsychotic-like efficacy without increasing raclopride-induced catalepsy. Similarly, pimavanserin (ACP-103), a 5-HT2A receptor inverse agonist, potentiated haloperidol's antipsychotic-like efficacy in animal models, but did not increase haloperidol-induced catalepsy. Pimavanserin was also shown to significantly decrease haloperidol- or risperidone-induced hyperprolactinemia in animal models. As adjunctive to antipsychotics in patients with schizophrenia, pimavanserin enhanced the efficacy of a low subtherapeutic dose of risperidone without increasing motor side effects, but did not enhance the efficacy of a low therapeutic dose of haloperidol. Pimavanserin is not approved for use in schizophrenia. To date, no selective 5-HT2A receptor antagonists or inverse agonists have shown convincing antipsychotic efficacy as a monotherapy for the treatment of schizophrenia, but the pharmacological mechanism of blocking 5-HT2A receptors is thought to play an important role, together with D2 receptor blockade, in the efficacy of atypical

antipsychotics.

The serendipitous discovery of clozapine in the 1960s opened the second major chapter in the pharmacological treatment of schizophrenia. Clozapine exerted antipsychotic effects in humans with a markedly reduced risk of EPS or hyperprolactinemia at efficacious doses. This profile was sufficiently different from the first generation of antipsychotics that clozapine became the prototype of the so-called atypical antipsychotic drugs. Several second-generation antipsychotics were developed based upon clozapine, such as risperidone, olanzapine, quetiapine, paliperidone, ziprasidone, sertindole, iloperidone and lurasidone. These atypical antipsychotics have somewhat different pharmacological profiles, yet they all have antagonistic activity on dopaminergic D2 and serotonergic 5-HT2A receptors. These atypical antipsychotics can be divided mechanistically into those that bind to multiple other neuroreceptors, including modest affinity to D2 and 5-HT2A, such as clozapine, olanzapine and quetiapine, and those that exhibit potent D2 and 5-HT2A antagonistic activities, such as risperidone, paliperidone, sertindole and lurasidone, as summarised. Among these, SGA, clozapine and risperidone are the most widely used, and so these two antipsychotics were selected for extensive review and comparison with other generations of antipsychotic drugs, clozapine, risperidone and other second-generation antipsychotic drugs.