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Serotonergic approaches in the development of novel antipsychotics

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ABSTRACT

Schizophrenia is a chronic, debilitating neuropsychological disease characterised by positive, negative, and cognitive deficits. In recent years, new pharmacological treatment strategies have been developed to treat the sequalae of schizophrenia based upon more selective receptor activity profiles in the hope that treatment efficacy can be increased without inducing the side-effect profiles seen with current available therapies. One such strategy involves the development of combined (partial) 5-HT_{1A} agonists and D_2 receptor (partial) antagonists such as bifeprunox, SLV313, F15063 and SSR-181507 in an attempt to increase therapeutic efficacy of all symptom domains whilst alleviating adverse side effects. Other novel drugs including SLV310 and SLV314 combine selective serotonin reuptake inhibition (SSRI) functionality with D_2 receptor antagonism in an attempt to not only improve schizophrenic symptoms, but to also relieve other affective disorders intricately linked with the disorder. The main scope of this review will evaluate the major preclinical and clinical pharmacological findings concerning the aforementioned strategies and pharmacological agents, and compare their therapeutic potential with currently available antipsychotics; however, recent developments at other emerging serotonergic targets such as 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors will also be considered.

1. Introduction

Schizophrenia is a complex neuropsychiatric syndrome affecting approximately 1% of the population at any given time with many patients undergoing prolonged symptom-free periods of remission interspersed with repeated relapses into acute psychotic episodes (for reviews see Seeman and Kapur, 2000; Shapiro et al., 2003; Cuisiat et al., 2007; Newman-Tancredi et al., 2007b). The onset of the disease is usually seen post adolescence (16–25 years) with psychotic symptomatologies having a higher incidence in males than females, although the converse is seen in late–onset schizophrenia (40–60 years; see Howard et al., 2000; Aleman et al., 2003 for review). Classically, symptoms of the disease have been clustered into two main categories, namely the positive symptoms (auditory and visual hallucinations, delusions, conceptual disorganisation, thought disorder and some motor disturbances) and the negative symptoms (affective blunting, social withdrawal, anhedonia, avolition and poverty of thought and content of speech (for review see Andreasen, 1995)). In recent years, the cognitive impairments associated with the disease such as executive function, working memory and attentional deficits, disruptions of cognitive processing and mood disorders have emerged as an important separate symptom class requiring medical intervention (see Meltzer et al., 1999 for full review). Patients may present with any combination of this array of symptoms making diagnosis and treatment of the disease problematic. Moreover, the expression of co-morbid affective disorders, such as depression, compromises quality of life and increases relapse and suicide rates in patients (Meltzer, 1998; Siris, 2000; Möller, 2005).

2. Current therapeutic strategies used in the treatment of schizophrenia

Schizophrenia was first pharmacologically treated in the late 1950s by the use of the potent dopamine (DA) D_2 receptor antagonist haloperidol and other agents such as chlorpromazine which are thought to attenuate putative hyperdopaminergia of the mesolimbic pathway (Granger and Albu, 2005; López-Muñoz et al., 2005) thereby treating the positive symptoms of the disease. However, the simultaneous inhibition of nigrostriatal DA transmission resulted in severe adverse motoric and/or neurological side

Abbreviations: 8-OH-DPAT, 8-hydroxy-2-(di-*N*-propylamino)-tetralin; 5-HT, 5-hydroxytryptamine, serotonin; 5-HTP, 5-hydroxytryptophan; ACh, acetylcholine; CAR, conditioned avoidance response; DA, dopamine; EPS, extrapyramidal symptoms; MK801, (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate; (m)PFC, (medial) prefrontal cortex; PCP, phencyclidine; NOR, novel object recognition; PPI, prepulse inhibition; SSRI, selective serotonin reuptake inhibitor; SNC, substantia nigra pars compacta; USV, ultrasonic vocalisation; VTA, ventral tegmental area; WAY100635, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-*N*-(2-pyridinyl)cyclohexanecarboxamide).

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effects known as extrapyramidal side effects (EPS; tardive dyskinesia, dystonia, akathisia and parkinsonism) which occur when approximately 80% of striatal D_2 receptors are occupied (Seeman et al., 1976; Seeman and Kapur, 2000). The use of D_2 receptor antagonists can also induce hyperprolactinaemia potentially resulting in sexual dysfunction, infertility, galactorrhoea, amenorrhoea and osteoporosis (for full review see Langer and Sachar, 1977; Halbreich et al., 2003; Kinon et al., 2003). Consequently, the adverse effects associated with typical antipsychotics coupled with limited therapeutic efficacy against the negative and cognitive symptoms of schizophrenia may account for both increased non-compliance and relapse rates in patients.

Second generation or so-called "atypical" antipsychotics were developed which not only have considerable efficacy for the treatment of positive symptoms of the disease, but have also proven clinical efficacy within negative and cognitive domains (Meltzer, 1999). With the exception of amisulpride, it is generally accepted that the newer generation of antipsychotic agents such as clozapine, ziprasidone, risperidone, olanzapine, quetiapine, nemonapride and aripiprazole achieve an improved therapeutic profile via actions at diverse non-dopaminergic targets such as serotonergic, noradrenergic and muscarinic receptors whilst maintaining D_2 receptor antagonist functionality (Meltzer et al., 1989, 2003; Seeger et al., 1995; Scotte et al., 1996; Bymaster et al., 1996, 1999; Satoh et al., 1997; Schoemaker et al., 1997; Ichikawa and Meltzer, 1999; Shapiro et al., 2003). The richer pharmacological activity of atypical antipsychotics compared with the D_2-receptor selective typical antipsychotics may account for their ability to treat a wider range of schizophrenic symptoms but with lower propensities to induce adverse EPS both pre-clinically and clinically (Meltzer, 1999; Meltzer et al., 2003). However, atypical antipsychotics are not without side-effect limitations which range from metabolic disorders such as weight gain, hyperglycaemia and dyslipidaemia and additional cardiovascular sequalae such as cardiac arrhythmia and high blood pressure. Furthermore, dose-dependent EPS and hyperprolactinaemia are still observed with certain compounds and clozapine is associated with a well-documented incidence of agranulocytosis (Hasegawa et al., 1994; Meltzer, 1994; Allison et al., 1999; Kasper et al., 1999; Haddad, 2005; Haupt, 2006). Novel treatment strategies are now focusing upon more selective receptor activity in order to improve efficacy and side-effect profiles.

3. Combined dopamine D_2 receptor antagonists or partial agonists and 5-HT_{1A} receptor agonists as novel atypical antipsychotics

The antipsychotics risperidone, olanzapine and haloperidol have limited affinity for 5-HT_{1A} receptors (Newman-Tancredi et al., 2005, 2007b; McCreary et al., 2007). However, ziprasidone, clozapine, nemonapride and aripiprazole have been described as putative 5-HT_{1A} receptor (partial) agonists when tested in vitro (Mason and Reynolds, 1992; Newman-Tancredi et al., 1996, 1998, 2005; Burris et al., 2002; Jordan et al., 2002; Shapiro et al., 2003; Tadori et al., 2005; Cosi et al., 2006). Whilst this has not always translated into in vivo 5-HT_{1A} agonist effects (Lejeune et al., 1994; Assié et al., 1997, 2005; Jordan et al., 2004; Zocchi et al., 2005; McCreary et al., 2007), some studies do suggest that these antipsychotics do have intrinsic activity at 5-HT_{1A} receptors in vivo (Bartoszyk et al., 1996; Assié et al., 1997; Rollema et al., 1997; Millan et al., 1998; Ichikawa and Meltzer, 1999; Sprouse et al., 1999; Dahan et al., 2006; Bortolozzi, et al., 2007).

More specifically, the anticataleptogenic properties of both clozapine and nemonapride have been found to be partially 5-HT_{1A} receptor-mediated (Millan et al., 1998; Prinssen et al., 1998). In addition, clozapine has been found to preferentially elevate DA and noradrenaline levels in the prefrontal cortex (PFC; compared to subcortical regions) via 5-HT_{1A}-dependent mechanisms (Rollema et al., 1997; Millan et al., 1998). Of significant interest is the ability of clozapine to reverse neuroleptic-induced catalepsy, and to modulate frontocortical DA release which is reversed by the selective 5-HT_{1A} receptor antagonist WAY100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-*N*-(2-pyridinyl)cyclohexanecarboxamide) (Rollema et al., 1997; Millan et al., 1998). Given that 5-HT_{1A} receptor agonism is also known to alter anxiety states and mood both clinically and preclinically (Blier and Ward, 2003), it is noteworthy that clozapine inhibited ultrasonic vocalisations in a rat model of anxiety via 5-HT_{1A} receptor dependent mechanisms (Bartoszyk et al., 1996). Thus, activation of 5-HT_{1A} receptors likely contributes to its efficacy in schizophrenia (Bartoszyk et al., 1996; Rollema et al., 1997; Millan et al., 1998; Millan, 2000).

Drawing on the 5-HT_{1A} receptor (partial) agonist activities of such antipsychotics as clozapine, nemonapride and aripiprazole, a number of new chemical entities acting as "selective" 5-HT_{1A} receptor (partial) agonists and D_2 receptor (partial) (ant)agonists have been described. Such molecules demonstrate significant preclinical, and in some cases clinical efficacy against the positive, negative and cognitive deficits associated with schizophrenia whilst simultaneously reducing the propensity for EPS (Kleven et al., 2005; Bardin et al., 2006a,b; 2007; Newman-Tancredi et al., 2007b). As presented in Table 1, the compounds which have shown the most preclinical and/or clinical potential are the partial D_2-like and 5-HT_{1A} receptor agonists bifeprunox (Feenstra et al., 2001; Hesselink et al., 2003; Hertel et al., 2005) and SSR-181507 (Claustre et al., 2003; Depoortère et al., 2003) and the full D_2-like antagonists and 5-HT_{1A} receptor (partial) agonists SLV313 (McCreary et al., 2007), F15603 (Assié et al., 2007; Cuisiat et al., 2007; Depoortère et al., 2007a,b; Newman-Tancredi et al., 2007a) and S16924 (Millan et al., 1998).

One of the earliest novel compounds capitalising on a more selective receptor activity profile compared to clozapine was S16924. Like other antipsychotics, S16924 had modest binding at D_2-like receptors where it acted as an antagonist, and also had potent affinities for 5-HT_{1A} receptors but also possessed 5-$HT_{2A/2C}$ antagonist properties (Millan et al., 1998). Unlike clozapine, however, S16924 demonstrates no affinity for histaminergic and/or muscarinic receptors (Millan et al., 1998). S16924 was shown to possess a favourable preclinical therapeutic profile against positive and negative symptoms of schizophrenia in animal models without the induction of catalepsy (Tables 1 and 2); however, no clinical data are available.

Another compound in early clinical development for schizophrenia is the "selectively non-selective" D_3/D_2 dopamine receptor antagonist/partial agonist with 5-HT_{1A} receptor affinity (2.5 μM) RGH-188 (Gyertyán et al., 2006; Laszlovszky et al., 2008). Recent findings suggest that RGH-188 may show a favourable therapeutic profile when compared to more traditional antipsychotics; however more comprehensive preclinical data (e.g. data which demonstrates in vivo efficacy at the 5-HT_{1A} receptor) are required before its profile can be directly compared with other 5-HT_{1A} receptor agonists and D_2 receptor antagonists/partial agonists.

Preclinical studies indicate that the pharmacological effects seen with such molecules present potential beneficial therapeutic effects but with reduced propensity for the side effects associated with other antipsychotic medications.

3.1. Rationale for using 5-HT_{1A} receptors as therapeutic targets for schizophrenia

It was originally hypothesised that potent 5-HT_{2A} receptor antagonism coupled with weaker D_2 receptor antagonism was the principle pharmacological feature distinguishing atypical from typical antipsychotics (Meltzer et al., 1989) many clinically relevant