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Atypical Antipsychotics and Inverse Agonism at 5-HT$_2$ Receptors

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Abstract

It is now well accepted that receptors can regulate cellular signaling pathways in the absence of a stimulating ligand, and inverse agonists can reduce this ligand-independent or "constitutive" receptor activity. Both the serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors have demonstrated constitutive receptor activity *in vitro* and *in vivo*. Each has been identified as a target for the treatment of schizophrenia. Further, most, if not all, atypical antipsychotic drugs have inverse agonist properties at both 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors. This paper describes our current knowledge of inverse agonism of atypical antipsychotics at 5-HT$_{2A/2C}$ receptor subtypes *in vitro* and *in vivo*. Exploiting inverse agonist properties of antipsychotic drugs may provide new avenues for drug development.

Keywords

Antipsychotic drugs; atypical antipsychotic drugs; inverse agonism; constitutive activity; serotonin; 5-HT$_{2A}$ receptors; 5-HT$_{2C}$ receptors; schizophrenia

SEROTONIN RECEPTORS

Serotonin (5-hydroxytryptamine, 5-HT) is a biogenic monoamine with paracrine, neurocrine, and hormonal functions (for reviews see [1–3]). These effects are mediated by a variety of serotonin receptors within seven families (5-HT$_1$ to 5-HT$_7$), which are further divided into multiple subtypes. The 5-HT$_2$ receptor family is comprised of three subtypes: 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$. Drugs with affinity for 5-HT$_{2A/2C}$ receptors have been used as treatments for disorders such as schizophrenia [4–6], depression [7, 8], and more recently insomnia (SR46349B and M100, 907, see clinicaltrials.gov) [9]. Importantly, evidence has suggested that the effects of these medications are mediated through inverse agonism at 5-HT$_{2A}$ and/or 5-HT$_{2C}$ receptors [6, 8, 10].

Of the seven types of 5-HT receptors, all are G-protein coupled receptors (GPCRs), except for the ion channel-associated 5-HT$_3$ receptors. Within each subfamily, 5-HT receptors can share pharmacological and biochemical characteristics while remaining distinct from one another. For example, 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors have a high degree of amino acid

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

homology and can regulate similar cellular signaling pathways (reviewed in [11, 12]), but differences between the two receptors have been reported [13–14]. In terms of similarities, both are GPCRs that function through an association with the G protein, $G_{q/11}$, among other transducing molecules. When an agonist, such as 5-HT, binds to 5-HT_{2A} or 5-HT_{2C} receptors, it leads to the activation of phospholipases such as phospholipase C [PLC] and phospholipase A_2 [PLA_2] and increases in inositol trisphosphate and intracellular Ca^{2+} and the release of free arachidonic acid [15–19]. In addition to these agonist-elicited effects via 5-HT_2 receptors, studies have shown that similarities in the cellular and behavioral effects are produced in response to inverse agonists at 5-HT_{2A} and 5-HT_{2C} receptors. Indeed, much of the evidence in favor of 5-HT_{2A} and 5-HT_{2C} receptor inverse agonism derives from work with atypical antipsychotics (reviewed below), which has led to the hypothesis that atypical antipsychotics alleviate symptoms of schizophrenia as a consequence of their inverse agonist properties at 5-HT_2 receptors.

CONSTITUTIVE RECEPTOR ACTIVITY AND INVERSE AGONIST EFFICACY

The discovery of inverse agonism was based on the pioneering work of Cerione and colleagues [20, 21] and further research by Costa and Herz [22]. These studies showed that in receptor systems, there is a spontaneous formation of active receptor conformations that produce measurable responses in the absence of a stimulating ligand (i.e., agonist), which is now referred to as constitutive or ligand-independent receptor activity. Ligands that were able to reduce this constitutive activity were defined as inverse agonists (for review see [23, 24].) It is now generally accepted that many receptor systems can be constitutively active [25]. Moreover, many ligands that were first characterized as receptor antagonists, including over 80% of the classical GPCR antagonists, exhibit inverse agonism [23, 24]. Although the early experiments of Cerione et al. and of Costa and Herz led to the development of the two-state model of receptor function, where receptors in a population were in equilibrium between an inactive and an active receptor conformation capable of eliciting a cellular response in the absence of a ligand, subsequent studies have resulted in the modification of the two-state model such that receptors can exist in more than one active conformation (multi-active state models). In these multi-active state models, such as the three-state model shown in Fig. 1, constitutive receptor activity, and inverse agonism, is dependent upon the response measured.

In the three-state model (as developed by Kenakin [23] and Leff [26]) and shown in Fig. 1, the receptor can exist in either an inactive conformation (R) or in one of two active conformations (R^* or R^{**}). These active forms can produce a response in the absence of an agonist (e.g. the constitutive activity), and the proportion of receptors in these states is determined by allosteric transition constants, L and M. Since L and M can differ, the magnitude of constitutive receptor activity can differ depending upon the response measured. When a ligand (A) is introduced, it binds to the receptor conformations according to the magnitude of the various affinity constants, KA, KA* and KA**. If the ligand has a higher affinity for one, or both, of the active conformations, it will enrich the proportion of the receptor population in that active conformation and thus increase the magnitude of response, acting as an agonist. If, on the other hand, the ligand has preferential affinity for the inactive conformation (R), it will enrich the population of inactive receptor, by depleting

one or both of the active conformation. In this case, by depleting the quantity of an active receptor conformation, the response associated with that conformation will decrease and the ligand will be an inverse agonist for that response. In this model, ligand efficacy can be defined as the ratio of the affinity constant for the inactive receptor conformation (KA) to that of either of the active conformations (KA* or KA**). If the KA/KA* or KA/KA** ratio is less than one, the ligand will behave as an agonist (enriching the proportion of the active receptor conformation) for that response. On the other hand, if the KA/KA* or KA/KA** ratio is greater than 1, the ligand will behave as an inverse agonist for that response. The magnitude of efficacy (as an agonist or an inverse agonist) is based upon the magnitude of the difference in affinity constant. In this model of receptor function, drugs that are antagonists are relatively rare, as they must have equal affinity for all receptor conformations (KA/KA* and KA/KA** ratios of 1) and therefore do not alter the quantity of R* or R** and thus do not change the level of ongoing response associated with either receptor conformation.

As shown in Fig. 1, the three-state model of receptor function also takes into account the fact that a single receptor with different active receptor conformations can regulate more than one response pathway (represented as “Response 1” and “Response 2”). Thus, in receptor systems, there can be preferential activity toward a given response depending on the proportion of receptors in the corresponding active conformations. This would affect not only basal activity of the system (constitutive activity of response 1 greater than that of response 2) but also ligand-dependent activation or inactivation. Notably, the relative efficacy of ligands to regulate the multiple signaling pathways can differ. For example, a ligand could be an agonist for one response, but an inverse agonist for another. This phenomenon of response-dependent relative efficacy has been described using a number of terms including “stimulus-trafficking” “biased agonism” and “functional selectivity” (reviewed in [27]).

Functional selectivity is based upon ligands having differential efficacy for different signaling pathways coupled to a receptor in cells, therefore measurement of response-dependent ligand efficacy allows for assessment of functional selectivity properties of ligands. In certain circumstances where potency is influenced by efficacy, functional selectivity can be revealed as response-dependent potency differences. However, this situation occurs only for agonist ligands and only for those agonists for which there is a high efficiency of receptor-effector coupling (i.e. full agonists with “receptor reserve”). For weaker partial agonists, maximal response (E_{max}) reflects efficacy and therefore response-dependent E_{max} values reflect functional selectivity. For inverse agonists, “efficacy” is based upon their ability to promote receptor inactivation (e.g., to stabilize inactive conformations) and thereby reduce ligand-independent receptor-mediated signaling. Since potency of inverse agonists is not affected by efficacy, functional selectivity is reflected solely by response-dependent E_{max} values. Importantly, this allows for the use of relative efficacy comparison between signaling pathways using maximal responses as a measure of inverse agonist functional selectivity. In this manner, a recent study showed differences in the signaling profiles of two antipsychotic drugs (risperidone and paliperidone), which displayed inverse agonist properties for some (but not all) 5-HT_2 receptor –mediated signaling pathways [28].

The degree of ligand-independent or constitutive receptor activity for a given receptor-effector pathway can most easily be measured as the magnitude of the reduction of basal effector activity produced by a full inverse agonist. The initial methods to detect inverse agonism in GPCR systems incorporated measures of reduction in basal [^{35}S]GTPγS activity to assess constitutive receptor activity toward G protein activation [29–31], as well as various functional assays of changes in downstream basal effector signaling (e.g., PLC) [32]. Using these techniques, ligands could be classified as receptor agonists, inverse agonists, or neutral antagonists, for the measured pathway. As described above, agonists and inverse agonists are ligands that either increase or decrease basal effector responses, respectively, whereas antagonists are ligands that, on their own, do not alter the basal response, but block the effects of either an agonist or an inverse agonist. Measurements of inverse agonist-mediated reduction in basal effector activity depend on the level of constitutive activity of the system and thus are infl-uenced directly by the level of receptor expression and efficiency of receptor-effector coupling [33–35]. To observe inverse agonism, it is necessary that the receptor system produces a measurable basal effector response and therefore is not useful in systems with little to no basal activity. Given this, the majority of the foundational inverse agonist research has involved studies using transfected or mutated cells with a high expression of receptors to produce a high basal activity *in vitro* to allow visualization of inverse agonist properties of ligands. Using this approach, 5-HT$_{2C}$ receptors have been shown to have constitutive activity in transfected cell lines, but it has proven more difficult to show constitutive receptor activity in native tissue or in a behavioral assay (for review of 5-HT$_2$ receptor inverse agonism see [10] and [36]). Interestingly, the reverse is true for detecting constitutive receptor activity of 5-HT$_{2A}$ receptors as inverse agonism at 5-HT$_{2A}$ receptors has been more readily detected *in vivo* [37]. Importantly, as basal activity is not as pronounced in some receptor systems, a particularly sensitive method for detecting constitutive receptor activity and inverse agonist efficacy is by determining the effects of prolonged inverse agonist treatment on a given receptor-effector response.

Similarly to agonist stimulation, prolonged ligand-independent receptor activity can lead to a reduction of effector activity. Thus receptor signaling systems can exist in a state of constitutive, partial desensitization as a result ligand-independent receptor activity toward desensitization mechanisms. Prolonged (e.g. >4 h) treatment with an inverse agonist can promote re-sensitization of the receptor-effector response that may be visualized by enhanced responsiveness to agonist stimulation following washout of the inverse agonist. This second and very sensitive method for detection of inverse agonism has been used to study inverse agonist functional selectivity at 5-HT$_2$ receptors [28, 32, 36, 38].

5-HT$_2$ RECEPTOR CONSTITUTIVE ACTIVITY AND INVERSE AGONISM

In Vitro studies

In vitro heterologous expression systems have proven instrumental for the study of inverse agonism and constitutive activity for a variety of receptors including 5-HT$_2$ receptors. Moreover, they have shown that measures of inverse agonist efficacy and constitutive receptor activity are not only dependent on the signaling pathway but also on the cell background in which the receptors are expressed. Multiple researchers have reported

agonist-independent receptor activity toward PLC activity for 5-HT_{2C} receptors [32, 39–43] as well as toward PLA_2 [19, 28, 32, 36]. The high degree of 5-HT_{2C} constitutive receptor activity toward PLC has provided a system for further characterization of functional selectivity and constitutive desensitization of the 5-HT_{2C} receptor system. As mentioned above, inverse agonists have the ability to reduce constitutive desensitization. Berg and colleagues [32] showed that in CHO cells expressing 5-HT_{2C} receptors, prolonged treatment with 5-HT_{2C} inverse agonists differentially increased receptor responsiveness for PLC, but not PLA_2 which indicates that constitutive receptor activities toward desensitization pathways can also differ, depending upon the response measured. Further, these studies were the first to show that the 5-HT_{2C} receptor does not exhibit a high degree of constitutive activation for all downstream pathways. For example, the constitutive 5-HT_{2C} receptor activity for the PLA_2 pathway is much less than that of PLC [32], subsequently, inverse agonist efficacy at the 5-HT_{2C} receptor is also greater for PLC compared to PLA_2 responses [32, 36].

As mentioned above, constitutive activity of the 5-HT_{2A} receptors toward PLC activity has not been readily detected unless the receptor was mutated [44–46] or measured in systems with overexpression of associated G proteins [6]. Although constitutive 5-HT_{2A} receptor activity for PLC is weak, higher constitutive activity has been reported for a reporter gene assay (Receptor Selection and Amplification Technology (R-SAT)) [6, 45] which suggests that, like the 5-HT_{2C} receptor, constitutive activity of 5-HT_{2A} receptors also differs with the signaling pathway studied.

In Vivo Studies

Among the first supporting evidence for 5-HT_2 receptor inverse agonism *in vivo* came from studies demonstrating the varying effects of 5-HT_{2A} receptor agonists, neutral antagonists, and inverse agonists on learning (for review see [37]). These drugs could be classified on the basis of whether they enhanced (agonists), had no effect (antagonists), or inhibited (inverse agonists) conditioned responses in the rabbit eyeblink model. The results of these experiments confirmed that native (non-mutated) 5-HT_{2A} receptors were indeed constitutively active and identified previously well-characterized antagonists as inverse agonists, including ritanserin, MDL11939 and M100907. Moreover, these studies established the rabbit eyeblink model as a tool for monitoring inverse agonism at a systems level. Further studies by the Harvey group characterized the effects of chronic inverse agonist treatment on 5-HT_{2A} receptor density [47, 48]. When rabbits were repeatedly administered the inverse agonists MDL11939 and M100, 907, there was a resultant increase in 5-HT_{2A} receptor expression as measured by radioligand binding [47, 48]. Moreover, there were corresponding behavioral effects as a consequence of the receptor up-regulation. Following repeated treatment with the inverse agonists, there was an increase in the rate of learning response [47].

Additional evidence for effects of 5-HT_2 receptor inverse agonism *in vivo* involves the regulation of dopamine release. Both 5-HT_{2A} and 5-HT_{2C} receptors have been shown to modulate dopamine release in the brain [49–53]. For example, the well-characterized 5-HT_{2C} receptor inverse agonist, SB206553, increased dopamine levels in the nucleus

accumbens that was blocked by the neutral antagonist, SB 242084 [53]. Similarly, the 5-HT_{2A} receptor inverse agonists, M100907 and SR46349B, have been shown to increase the release of dopamine in mesolimbic and mesocortical brain regions [51–52, 54–56]. Moreover, inverse agonist action at 5-HT_{2C} and 5-HT_{2A} receptors may converge downstream at the level of dopamine release. In studies with atypical antipsychotics, mesocortical dopamine release was enhanced [57]. Given that most if not all atypical antipsychotics have inverse agonist properties at 5-HT_{2C} and 5-HT_{2A} receptors (see discussion below), it has been proposed that inverse agonist activity at both these receptors contribute to alleviate the negative symptoms and cognitive deficits observed in schizophrenia [58].

SCHIZOPHRENIA AND 5-HT_2 RECEPTORS

First Generation Antipsychotics

Schizophrenia is a severe mental disorder characterized by delusions, hallucinations, disorganized speech, cognitive deficits and affective symptoms. Although schizophrenia was first described over a century ago, in the intervening years, treatments for schizophrenia still have not progressed to a point where all symptoms are controlled. Furthermore, despite the number of treatment options available, schizophrenia remains one of the leading causes of disability in the world [59]. Schizophrenia is defined by indications that can be divided into four groups: positive, negative, cognitive, and mood-related. Positive and negative symptoms are described based on the idea that “positive” refers to extra behaviors observed in the patient population whereas “negative” refers to behaviors or emotions that are “missing.” Positive symptoms are among those most commonly associated with schizophrenia and can include hallucinations, delusions, and paranoia. Negative symptoms include flat affect, ambivalence, social withdraw, and anhedonia. The cognitive effects generally involve deficits in both learning and memory. Finally, mood-related symptoms include anxiety, depression, agitation, and/or suicidality. It is important that even with this diverse symptomatology, all antipsychotics currently on the market mainly target the psychosis associated with schizophrenia [60].

Hallucinations and delusions are only two symptoms of schizophrenia, but they are representative of the characteristic change in perception exhibited in patients. The first drugs approved to treat schizophrenia and diminish psychosis were traditionally dopamine antagonists. Of these “typical” or “first generation” antipsychotics, haloperidol was the most efficacious. Unfortunately, there were significant problems associated with the use of haloperidol, such as cardiac events, tardive dyskinesia or extrapyramidal side effects including tremor, akathisia (inability to sit still), dystonia (twisting or repetitive motions), and slurred speech (for review see [61]). As these drugs were dopamine D_2 receptor antagonists, it was thought that their actions at D_2 receptors contributed to both the benefits and adverse motor effects. Subsequently, because of the adverse effects associated with typical antipsychotics, second-generation or “atypical” antipsychotics were developed.

Second Generation Antipsychotics

The second generation of antipsychotics were found to have lower risk of extrapyramidal side effects and tardive dyskinesias and thus are referred to as “atypical”. Although antagonism or weak efficacy at dopamine D_2 receptors appears essential for antipsychotic activity, the complete molecular mechanism that underlies the therapeutic efficacy of atypical antipsychotic drugs is still unknown. Several theories have been postulated to account for atypicality, including 1) higher affinity for 5-HT_{2A} receptors than for dopamine D_2 receptors (i.e., the Meltzer hypothesis), 2) faster off-rate of binding to D_2 receptors, and 3) agonism at presynaptic versus antagonism at post-synaptic D_2 receptors (for example aripiprazole) [62]. Although these drugs produce fewer extrapyramidal side effects, some, if not most, were found to exhibit significant metabolic side-effects including weight gain, hyperglycemia, dyslipidemia [63], and in the case of clozapine, an increased risk of agranulocytosis (reviewed in [61]). Since in addition to binding D_2 and 5-HT_2 receptors, these drugs bind to multiple receptor subtypes, including alpha 1 adrenergic and H1 histamine receptors, it is possible that some adverse effects are a result of “off-target” signaling of these receptor systems [64].

Atypical antipsychotics used to treat schizophrenia have been shown to increase the release of dopamine in the prefrontal cortex, and 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1A} receptors have been shown to mediate this effect [65]. Furthermore, clozapine, olanzapine, quetiapine (see Table 1), and other atypical antipsychotics have high affinities not only for 5-HT_{2A}, but also 5-HT_{2C} receptors [66]. Thus, an alternative approach may be to indirectly modulate dopamine levels through 5-$HT_{2A/2C}$ receptor inverse agonism (discussed below) that may effectively manage the positive symptoms of schizophrenia leading to a more effective therapeutic strategy.

ATYPICAL ANTIPSYCHOTICS AS 5-HT_2 RECEPTOR INVERSE AGONISTS

As described above, many studies have shown inverse agonism for 5-HT_2 receptor ligands. Once discovered, researchers were interested in examining whether atypical antipsychotics, which had known binding affinity for 5-HT_2 receptors, also had inverse agonist effects at those receptors. Clozapine was the first FDA approved atypical antipsychotic that was distinct from the typical antipsychotics in that it had high affinity for 5-HT_2 receptors and was classified as an antagonist at these receptors. Upon further investigation, Westphal and Sanders-Bush [67] were among the first to present evidence of functional inverse agonism at the 5-HT_{2C} with clozapine in a heterologous system (NIH/3T3 fibroblasts). They demonstrated that as an inverse agonist, clozapine had functional effects and receptor binding characteristics that were opposite that of 5-HT_2 agonists. For example, clozapine, as an inverse agonist, bound the inactive (uncoupled) form of 5-HT_{2C} with a high affinity; by contrast, agonists had a higher affinity for the active (G-protein coupled) form of the 5-HT_{2C} receptor. Additional studies that examined the effects of the atypical antipsychotics clozapine, olanzapine, and risperidone also found that they had inverse agonist properties at 5-HT_{2C} receptors *in vitro*. Interestingly, all *atypical* antipsychotic drugs tested displayed inverse agonist activity at 5-HT_{2C} receptors, whereas almost all of the *typical* antipsychotics only displayed antagonist properties in this system [43]. Inverse agonism of clozapine *in*

vivo has also been reported using microdialysis techniques in a manner similar to the initial studies that described 5-HT_2 inverse agonism. Specifically, clozapine increased dopamine release in the nucleus accumbens and striatum, which indicates that clozapine has inverse agonist activity at the 5-HT_{2C} receptor *in vivo* [68]. Combined, these data lead to the hypothesis that 5-HT_{2C} inverse agonism may play a role in the therapeutic effects of atypical antipsychotics.

As mentioned above, olanzapine, an atypical antipsychotic approved in 1996 (six years after clozapine), has also been shown to have inverse agonist activity at 5-HT_2 receptors. Again, these studies utilized a heterologous system of cells expressing a human isoform of 5-HT_2 receptors. In CHO cells, Zhang and colleagues [69] report that olanzapine exhibited inverse agonism at the INI isoform of the 5-HT_{2C} receptor as defined by a decrease in 5-HT_{2C} receptor-mediated calcium signaling. However, conflicting results have been reported when the 5-HT_{2C} receptor is expressed in a different cell background (HEK-293 cells). Rauser and colleagues [70] found that several drugs without antipsychotic properties and many typical antipsychotics were inverse agonists at the human 5-HT_{2C} receptors. These variations across experimental approaches confirm that observations of inverse agonism can be dependent on both the signaling pathway measured and the cell phenotype in which the receptors are expressed.

Clozapine was also reported to be an inverse agonist at the 5-HT_{2A} receptor [44, 71]. These studies utilized mutated 5-HT_{2A} receptors and measured stimulation of the PLC pathway. Certain mutations produced 5-HT_{2A} receptors with a high degree of constitutive receptor activity. The antipsychotic clozapine was able to decrease this basal response indicating its inverse agonist properties at the 5-HT_{2A} receptor. The atypical antipsychotic, risperidone, has also been characterized as a 5-HT_{2A} receptor inverse agonist. Similar to clozapine, *in vitro* risperidone produced a significant reduction in basal PLC activity in a system with a high level of constitutively active 5-HT_{2A} receptors [44].

Despite having similar inverse agonist properties at 5-HT_2 receptors, the atypical antipsychotics also produce distinct cellular signaling profiles. As discussed above, inverse agonists can also display functional selectivity. Interestingly, differences between atypical antipsychotics have been recently described when comparing risperidone and paliperidone [28]. Risperidone is an atypical antipsychotic approved for use in the clinic in 1993. Paliperidone (approved in 2006) is the major active metabolite of risperidone, differing by only a single hydroxyl group. Both paliperidone and risperidone display simple, competitive antagonism in radioligand binding assays with similar affinities for their target receptors [72–74]; however, there have been some reports of differences in therapeutic effects between the two drugs [75–77], In a variety of heterologous systems expressing 5-HT_{2A} or 5-HT_{2C} receptors, it was determined that there were distinct differences in the efficacy of these two drugs for a number of signaling responses [28]. Since the two drugs have different therapeutic effects, differences at the signaling level could have important implications for variations observed in the clinic. Further, these results are consistent with the idea that inverse agonist properties at 5-HT_2 receptors may contribute to therapeutic efficacy of atypical antipsychotics.

More recently, a potent 5-HT_2 receptor inverse agonist, pimavanserin (ACP-103) was developed as a lead compound for a new avenue of potential antipsychotic treatments. In 2006, *in vitro* studies utilizing a heterologous system expressing human 5-HT_2 receptors first described inverse agonism of pimavanserin at both 5-HT_{2A} and 5-HT_{2C} receptors [78]. In behavioral studies, pimavanserin also reduced 5-HT_2-mediated behaviors suggesting it could be acting as either an antagonist or inverse agonist at 5-HT_2 receptors [78]. Using the R-SAT technique, the researchers were able to observe inverse agonism of basal 5-HT_2 responses and they concluded that the *in vivo* and *in vitro* effects were consistent with 5-HT_2 inverse agonism as a mechanism for antipsychotic-like efficacy [78]. Subsequent studies confirmed the effects of pimavanserin and reported a better side-effect profile in animal models predictive of antipsychotic activity [79–82] suggesting that inverse agonists targeting 5-HT_2 receptors may have improved antipsychotic efficacy and tolerability. However, although pimavanserin is reported to enhance the efficacy and tolerability of the atypical antipsychotic, risperidone, but not the typical antipsychotic, haloperidol [83], clinical trials conducted with pimavanserin monotherapy have been disappointing. By contrast, recent studies suggest that pimavanserin may be effective for treating the secondary psychosis associated with Parkinson's disease which is thought to be due to 5-HT_{2A} receptor activity [86, 87]. Currently, pimavanserin is in clinical trials for treatment of psychosis associated with Parkinson's disease [88 and see www.clinicaltrials.gov].

In addition to inverse agonism, it has been suggested that 5-HT_{2C} receptor agonists may be effective antipsychotics for treatment of schizophrenia and other psychiatric disorders [90]. For example, the preclinical profile of the selective 5-HT_{2C} receptor agonist, vabicaserin, indicated antipsychotic-like efficacy [91]. However, results of a Phase II trial with vabicaserin in comparison to olanzapine and placebo indicated that although the PANSS (positive and negative symptom scale) total scores for vabicaserin were improved at the low dose (200 mg) but not the higher dose (400 mg), the improvement was much lower than that of olanzapine. Further, the overall site ratings were not suggestive of clinical efficacy for vabicaserin [92]. Interestingly, using an updated quantitative systems pharmacology model to predict steady state clinical efficacy of vabicaserin as monotherapy, Liu *et al*, [92] reported that vabicaserin had limited clinical benefit for treatment of schizophrenia, consistent with the results of the Phase II clinical trial.

SUMMARY AND CONCLUSION

In summary, the potential for development of 5-HT_2 receptor inverse agonists as either front-line approaches for the treatment of psychosis or as adjuvant therapies for schizophrenia has been documented. However, although evidence suggests that therapeutic efficacy may be due to an inverse agonist property of a given ligand, in general, evidence supporting therapeutic relevance of inverse agonism is lacking in clinical settings (for review [84]) and the relevance of inverse agonist properties of atypical antipsychotics needs to be addressed further. Based on the lack of clinical efficacy for treatment of schizophrenia by selective 5-HT_{2A} receptor inverse agonists (e.g., pimavanserin) and the selective 5-HT_{2C} receptor agonist, vabicaserin, its intriguing to speculate that ligands that are selective for a single receptor subtype regardless of the drug property (i.e., agonist or inverse agonist) may not be therapeutically effective for treatment of diseases with multiple etiologies such as

schizophrenia. Interestingly, applications of 5-HT_2 receptor inverse agonists have recently extended beyond schizophrenia. For example, in addition to psychosis associated with Parkinson's disease [86], 5-HT_2 receptor inverse agonists are also being evaluated as treatments for psychosis related to Alzheimer's disease [85] and for treatment of movement disorders related to Parkinson's disease [87]. Overall, a better understanding of inverse agonism at 5-HT_2 receptor systems could have far-reaching implications for the development of novel therapeutics.

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LIST OF ABBREVIATIONS

5-HT_{2A}	serotonin 2A receptor subtype
5-HT_{2C}	serotonin 2C receptor subtype
G protein	guanine nucleotide binding protein
PLA_2	phospholipase A_2
PLC	phospholipase C

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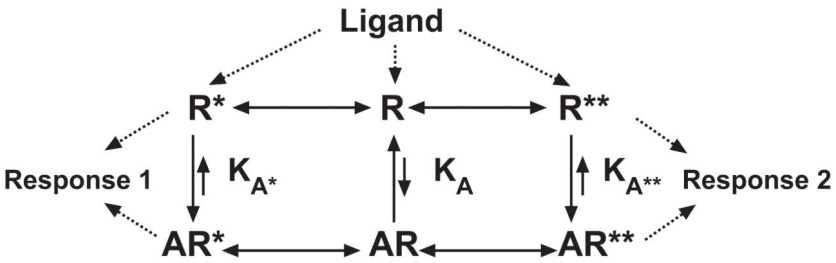

Fig. 1.

Three-state model of receptor function. Receptors can exist in an inactive conformation (R) or in multiple active conformations (two are shown: R^* or R^{**}). Active conformations can produce responses in the absence of a ligand (constitutive activity) or upon binding of a ligand (A). Agonists differentially stabilize an active conformation depending upon the value of the equilibrium dissociation constants K_A^* and K_A^{**} relative to the K_A. Conversely, inverse agonists stabilize the inactive conformation of a receptor. For neutral antagonists, there is no receptor state selectivity and the value of the equilibrium dissociation constants K_A^* and K_A^{**} will be equal to that of K_A. Berg *et al.* (2005) [36]**.

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Table 1

Atypical Antipsychotic Drugs.

Generic Name	Trade Name	FDA Approval (Year)	5-HT$_{2A}$/5-HT $_{2c}$ Inverse Agonism
Clozapine	Clozaril	1990	[32, 43]
Risperidone	Risperdal	1993	[28]
Olanzapine	Zyprexa	1996	[43, 69]
Quetiapine	Seroquel	1997	[89]**
Ziprasidone	Geodon	2001	[43]
Aripiprazole	Abilify	2002	[69]
Paliperidone	Invega	2006	[28]
Asenapine	Saphris	2009	NR
Iloperidone	Fanapt	2009	NR

Sources: National Institute of Mental Health (NIMH), Food and Drug Administration (FDA). Arranged in order of approval date.

** quetiapine is a dopamine D_2 receptor inverse agonist [89]. NR= not reported.