Improving the Treatment of Schizophrenia: Focus on Serotonin (5-HT)₁A Receptors

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ABSTRACT

Although antagonism of mesolimbic dopamine D₂ receptors by neuroleptics such as haloperidol attenuates positive symptoms of schizophrenia, a significant population of “resistant” patients fails to respond while negative and cognitive symptoms are little modified. Furthermore, concomitant blockade of striatal D₂ receptors is associated with extrapyramidal motor side effects. The superior “atypical” antipsychotic profile of clozapine appears to reside in its broad pattern of interaction with D₂ receptors and a diversity of other monoaminergic sites. In this regard, serotonergic mechanisms are of particular relevance both in view of their modulation of dopaminergic transmission and their key role in the control of mood, cognition, and motor behavior. While most attention has focused on potential advantages of preferential 5-HT₂A versus D₂ receptor blockade, 5-HT₁A receptors likewise represent a valid target for improved antipsychotic agents. In this regard, rather than selective agents, ligands interacting with both 5-HT₁A and D₂ receptors appear of interest. A modest level of efficacy appears optimal, that is, sufficient to engage highly sensitive 5-HT₁A autoreceptors while blocking their low-sensitivity postsynaptic counterparts. Such a profile may counter negative and cognitive symptoms, improve mood, diminish extrapyramidal 5-HT₁A motor side effects, and, perhaps, enhance efficacy in refractory patients. Notably, “partial agonist” properties of clozapine at 5-HT₁A receptors may contribute to its distinctive functional profile. However, notwithstanding this compelling body of experimental data, clinical studies of antipsychotics interacting with 5-HT₁A receptors are required to establish their genuine pertinence to the—hopefully improved—treatment of schizophrenia.

Schizophrenia, Dopamine Receptors, and Neuroleptics

The highly complex and heterogenous disorder of schizophrenia is characterized by a diversity of symptoms that cannot realistically be ascribed to a unitary, discrete neuroanatomical or neurochemical lesion: positive (delusions, hallucinations, etc.), negative (alogia, flattened affect, social withdrawal), and cognitive-attentional (sensory-gating, working, and verbal memory, etc.). Correspondingly, any one single mechanism of drug action is unlikely to correct this panoply of symptoms in the absence of disruptive side effects. Conventionally, schizophrenia has been treated with neuroleptics, such as haloperidol, which interact preferentially with dopaminergic systems. Reflecting the involvement of hyperactive (or hyper-reactive) mesolimbic dopaminergic pathways, blockade of limbic D₂ receptors improves positive symptoms (Brunello et al., 1995; Kapur et al., 2000). However, a significant population of resistant patients remains refractory to treatment, while concomitant antagonism of normosensitive, striatal D₂ receptors elicits extrapyramidal motor side effects. Furthermore, negative and cognitive symptoms are little improved, probably because they reflect, at least partially, diminished function of mesocortical dopaminergic projections (Knable and Weinberger, 1997). There are several strategies through which novel agents interacting principally with dopaminergic mechanisms might offer an improved antipsychotic profile: 1) low affinity, rapidly dissociating and/or “neutral” D₂ receptor antagonists which, in contrast to potent and slowly dissociating “inverse agonists”, such as haloperidol, may less markedly and durably perturb basal dopaminergic activity (Seeman and Tallarico, 1999; Kapur et al., 2000); 2) partial D₂/D₃ receptor agonists permitting dual presynaptic (via autoreceptors) and postsynaptic attenuation of mesolimbic dopaminergic trans-
mission (Lahti et al., 1998); 3) preferential antagonists at D₃ versus D₂ receptors—no currently employed antipsychotic agent distinguishes these sites (Brunello et al., 1995); and 4) regarding cognitive deficits, selective D₃ receptor antagonists or D₁ receptor agonists (Friedman et al., 1999).

Nonetheless, recent years have seen increasing commitment to the concept that nondopaminergic mechanisms play a crucial role in the pathogenesis and, potentially, improved treatment of schizophrenia (Brunello et al., 1995; Roth and Meltzer, 1995). One major factor underpinning this conviction is the atypical dibenzodiazepine, clozapine.

**Clozapine: A Multireceptorial, Monoaminergic, Atypical Antipsychotic**

Clozapine is active in many patients that are not responsive to neuroleptics and exerts antipsychotic activity in the virtual absence of an extrapyramidal motor syndrome (atypical profile). Furthermore, it moderates negative and cognitive symptoms in a subpopulation of patients and, generally, stabilizes mood (Brunello et al., 1995; Meltzer et al., 1999). Clozapine is not, however, an ideal agent because its use is associated (in a small minority of patients) with serious hemotoxicity, while its blockade of muscarinic and histaminergic receptors provokes marked cardiovascular-autonomic side effects (Cunningham-Owens, 1996).

The significance of antagonist properties of clozapine at mesolimbic D₂ receptors in the control of positive symptoms should not be neglected. In fact, at clinically relevant doses, clozapine may elicit lower (and, perhaps, more transient) D₂ receptor occupation than haloperidol (Seeman and Tallerico, 1999; Kapur et al., 2000), but such observations fail to provide a satisfactory explanation for the unique clinical profile of clozapine, which cannot as yet be attributed to a single receptorial mechanism. Indeed, clozapine interacts with a broad array of dopaminergic, serotonergic (and adrenergic) receptors, and this global receptorial profile may account for its distinctive pattern of clinical activity (Fig. 1) (Brunello et al., 1995; Millan et al., 1998a). Within this multireceptorial framework, the relatively pronounced interaction of clozapine at specific receptor types relative to its modest antagonist properties at D₂ receptor actions may be the key to its improved functional profile.

In accordance with this concept, while retaining significant antagonist properties at D₂ receptors, the incorporation of additional components of activity may permit optimization of beneficial versus deleterious properties. In this regard, serotonergic mechanisms have attracted particular interest, not in the least because the fifteen 5-HT types identified to date offer a broad palette of potential targets for novel, antipsychotic agents (Roth and Meltzer, 1995).

**Serotonergic Mechanisms in the Treatment of Schizophrenia**

Of this plethora of receptors, 5-HT₃, 5-HT₆, and 5-HT₇ subtypes have all been advocated as involved in the innovative mechanism of action of clozapine. However, data are limited and the arguments are not overly compelling (Brunello et al., 1995; Roth and Meltzer, 1995). On the other hand, hallucinogens stimulate 5-HT₂A receptors, and the relatively pronounced antagonist activity at 5-HT₂A versus D₂ receptors of clozapine and certain other antipsychotics may improve their therapeutic window concerning separation of antipsychotic from extrapyramidal side effects (Roth and Meltzer, 1995). Moreover, blockade of mesolimbic 5-HT₂A receptors by clozapine underlies its potent antagonism of the effects of phencyclidine, an agent unique in reproducing both

![Fig. 1. Radar representations of the binding profile of clozapine compared with haloperidol at multiple dopaminergic and serotonergic receptors. All data were generated in the author’s laboratory at cloned human (h) receptors, cloned rat (r) (5-HT₆ and 5-HT₇), and cloned mice (m) (5-HT₃) receptors. Note the broad-based and “equilibrated” interaction of clozapine at diverse dopaminergic and serotonergic sites, whereas haloperidol shows pronounced affinity for hD₂ (hD₃ and hD₄) receptors versus modest or weak affinity at other sites.](image-url)
positive and negative symptoms of schizophrenia in normal subjects (Millan et al., 1999). More recently, attention has focused on closely related 5-HT_{2A} receptors, which antipsychotics generally fail to discriminate from their 5-HT_{2A} counterparts (Brunello et al., 1995). Although it has been suggested that 5-HT_{2C} receptor blockade might compromise the benefits of 5-HT_{2A} receptor antagonism (Ichikawa and Meltzer, 1999), this contention underplays the prominent 5-HT_{2C} receptor antagonist properties of clozapine. Moreover, selective blockade of 5-HT_{2C} receptors reinforces frontocortical dopaminergic transmission, attenuates the extrapyramidal versus antipsychotic actions of haloperidol, and exerts anxiolytic properties, observations suggestive of a favorable influence in psychotic patients (Millan et al., 1998b, 2000; Reavill et al., 1999).

Irrespective of their relative importance, 5-HT_{2A} and 5-HT_{2C} receptors display functional interactions with 5-HT_{1A} receptors. For example, 5-HT_{2A} antagonists modify the influence of 5-HT_{1A} agonists upon dopaminergic transmission (Ichikawa and Meltzer, 1999) while 5-HT_{1A} agonists attenuate 5-HT_{2A} and 5-HT_{2C} receptor-mediated actions of hallucinogens (Schreiber et al., 1995). These findings raise the possibility that 5-HT_{1A} receptors may likewise be implicated in the pathogenesis and treatment of schizophrenia.

5-HT_{1A} Receptors: Neuronal Localization and Organization

5-HT_{1A} receptors are localized dendritically as inhibitory autoreceptors on serotonergic cell bodies of the median raphe nucleus (MRN), which predominantly innervates the dorsal hippocampus, septum and hypothalamus, and the dorsal raphe nucleus (DRN), which provides a major input to frontal cortex (FCX), ventral hippocampus, and striatum (Barnes and Sharp, 1999). In addition, postsynaptic 5-HT_{1A} sites are enriched in the FCX, hippocampus, and other corticollimbic structures implicated in the etiology of schizophrenia and in the actions of antipsychotic agents. In line with this organization, both pre- and postsynaptic 5-HT_{1A} receptors fulfill an important role in the modulation of mood, cognition, and motor behavior (Barnes and Sharp, 1999), functions perturbed in schizophrenic patients and profoundly affected by antipsychotic agents.

It is important to underline the greater sensitivity of 5-HT_{1A} autoreceptors compared with their postsynaptic counterparts (Barnes and Sharp, 1999). Correspondingly, certain drugs of intermediate efficacy simultaneously activate and antagonize dendritic and postsynaptic 5-HT_{1A} receptors, respectively (Fig. 2). As exemplified in the ensuing discussion, such partial agonist properties appear appropriate to the improved control of schizophrenia.

Three principal lines of evidence implicate 5-HT_{1A} receptors in the pathogenesis and management of schizophrenia: first, alterations in levels of 5-HT_{1A} receptors in schizophrenia; second, functional actions of selective ligands at 5-HT_{1A} receptors; and third, partial agonist properties of clozapine at 5-HT_{1A} receptors.

Alterations of 5-HT_{1A} Receptor Density in Schizophrenia: Neurodevelopmental Aspects

Studies of schizophrenic brain have identified a reproducible elevation in 5-HT_{1A} receptor density in FCX (Burnet et al., 1996, 1997; Gurevich and Joyce, 1997). This increase is independent of the radioligand and is not an effect of medication. Furthermore, it is specific to schizophrenia because depressed patients revealed a diminution in 5-HT_{1A} sites in a positron emission tomography (PET) study (Sargent et al., 2000), a technique that could instructively be applied to characterize 5-HT_{1A} receptors in the precocious phase of schizophrenia. The mechanism underlying the increase in 5-HT_{1A} receptor density remains uncertain but, because 5-HT_{2A} sites are decreased in parallel (Roth and Meltzer, 1995; Burnet et al., 1996), it is unlikely to reflect up-regulation due to deficient serotonergic transmission. In line with this assertion, no consistent alteration in extracellular levels of 5-HT has been documented in schizophrenics (Roth and Meltzer, 1995). Furthermore, levels of mRNA encoding 5-HT_{1A} receptors are not modified (Burnet et al., 1996), implying that post-transcriptional processes are involved. Challenge studies with the 5-HT_{1A} agonist, ipsapirone, revealed no marked change in 5-HT_{1A} receptor sensitivity in schizophrenics—although it is debatable to what extent endocrine parameters provide insights into the functional state of cortical 5-HT_{1A} receptors (Roth and Meltzer, 1995; Ichikawa and Meltzer, 1999). The pathophysiological significance of the increase in 5-HT_{1A} receptor density in schizophrenia, and its relationship to hypofrontality, remains, thus, to be elucidated. Furthermore, it needs to be established whether all schizophrenic patients, or only certain subpopulations, show elevations in frontocortical levels of 5-HT_{1A} receptors.

Interestingly, the alteration in frontocortical 5-HT_{1A} receptors is largely restricted to superficial laminae and likely includes a subpopulation localized on glutamatergic corticocortical neurones implicated in cognitive processes and possibly disrupted in schizophrenic patients (Francis et al., 1993; Burnet et al., 1996, 1997; see below). A comparable...
increase in 5-HT$_{1A}$ sites has been detected in orbital and temporal cortex, hippocampus, and nucleus accumbens but would profit from independent confirmation (Burnet et al., 1996). Interestingly, Burnet et al. (1997) reported an augmentation in the density of 5-HT$_{1A}$ autoreceptors in raphe nuclei, although functional correlates remain to be identified.

A final, intriguing finding was an elevation in levels of 5-HT$_{1A}$ receptors in the cerebellar vermis of schizophrenic patients, a structure implicated in sensory-attentional processes and motor function (Slater et al., 1998). This observation, which resembles the immature state, may reflect a failure to regress in maturity and be a consequence of neurodevelopmental abnormalities presaging schizophrenia. On the other hand, 5-HT$_{1A}$ receptors themselves exert a trophic role. Indeed, in both immature and adult brain, they can modify synaptic architecture and plasticity via interactions with astrocytes and neurones, including monoaminergic and cholinergic pathways (Riad et al., 1994; Azmitia et al., 1995). Thus, the possibility that 5-HT$_{1A}$ receptors might be causally involved in the aberrant, neurodevelopmental processes underlyng schizophrenia would be interesting to evaluate.

**Functional Actions of 5-HT$_{1A}$ Receptor Ligands**

**Relevance to Positive Symptoms.** 5-HT$_{1A}$ agonists attenuate induction of DA release in the nucleus accumbens by the psychostimulant, amphetamine (Ichikawa et al., 1995; Ichikawa and Meltzer, 1999). However, upon administration alone, in neurochemical and behavioral studies, no consistent pattern of data has emerged, with reports that they facilitate, suppress or fail to modify mesolimbic dopaminergic transmission (see Ichikawa and Meltzer, 1999; De La Garza and Cunningham, 2000; Millan et al., 2000). Furthermore, although 5-HT$_{1A}$ agonists block discriminative stimulus properties of amphetamine in primates (Nader and Woolverton, 1994), a complex pattern of effects has been obtained in rodents, including both attenuation and, albeit rarely, facilitation of the actions of amphetamine and cocaine (see Herges and Taylor, 1999; De La Garza and Cunningham, 2000).

Furthermore, 5-HT$_{1A}$ agonists modify neither conditioned avoidance responses in rats nor apomorphine-induced climbing in mice, “classic” models predictive of the control of positive symptoms (Evenden, 1992). Nonetheless, they potentiate the effects of haloperidol in these paradigms (Wadenberg, 1996; Prinsen et al., 1999). This action of 5-HT$_{1A}$ agonists is possibly related to their attenuation of neuroleptic-induced DA release in nucleus accumbens, which counts antagonism of postsynaptic limbic D$_2$ receptors (Ichikawa and Meltzer, 1999, 2000). Correspondingly, 5-HT$_{1A}$ agonist properties may enhance antipsychotic efficacy and/or afford activity in otherwise resistant patients.

Regarding paradigms modeling “sensory-gating” deficits of schizophrenia (filtering of irrelevant information), in contrast to antipsychotics, 5-HT$_{1A}$ agonists fail to either induce “latent inhibition” or to block the disruption of “prepulse inhibition” by propsychotic agents: these models involve mesolimbic dopaminergic pathways and are related to core, positive symptoms (Cassaday et al., 1993; Sipes and Geyer, 1995). Indeed, 5-HT$_{1A}$ agonists attenuate prepulse inhibition in rats, although the underlying mechanisms remain unclear (Sipes and Geyer, 1995) and an enhancement is seen in mice (Delawa et al., 2000). It would be of interest to examine the interaction of 5-HT$_{1A}$ ligands with haloperidol in such models.

Overall, selective activation (or blockade) of 5-HT$_{1A}$ receptors is unlikely to improve positive symptoms. However, stimulation of 5-HT$_{1A}$ autoreceptors may facilitate their control by neuroleptics, raising the possibility of improved management of refractory patients.

**Relevance to Negative and Cognitive Symptoms.** 5-HT$_{1A}$ receptor agonists consistently enhance the activity of the mesocortical dopaminergic pathway via actions expressed proximally to ventrotegmental dopaminergic cell bodies. Currently, the prevailing hypothesis is that engagement of 5-HT$_{1A}$ autoreceptors relieves a tonic, inhibitory influence of 5-HT$_{2C}$ receptors exerted via excitation of inhibitory GABAergic interneurones in the ventrotegmental area (Millan et al., 2000). In addition, GABAergic interneurones may be directly inhibited by postsynaptic 5-HT$_{1A}$ receptors, but evidence of this mechanism is weak, and it is probably of secondary importance (Millan et al., 2000).

These observations are of significance for several reasons. First, frontocortical dopaminergic pathways may inhibit mesolimbic dopaminergic pathways, suggesting a possible indirect (favorable) influence upon positive symptoms (Deutch, 1992; but see above). Second, within the FCX, DA plays a key role in cognitive processes that are compromised in schizophrenia; in particular, D$_1$ receptors participate in processes underlying working and other forms of memory (Friedman et al., 1999; Meltzer et al., 1999). Third, a functional perturbation of the FCX (“hypofrontality”), involving a disruption of dopaminergic input, is involved in the negative features of schizophrenia (Knable and Weinberger, 1997).

In a similar fashion, activation of 5-HT$_{1A}$ autoreceptors disinhibits locus coeruleus-derived, frontocortical adrenergic projections, which are subject to tonic, inhibitory control via 5-HT$_{2C}$ receptors (Millan et al., 2000). Adrenergic mechanisms in the FCX exerted predominantly via a$_1$-adrenoceptors (ARs) and, possibly, b$_{2-1}/$b$_{2a}$-ARs play an important role in processes underlying cognition, attention, and mood; indeed, they may be implicated in cognitive deficits associated with hypofrontality (Friedman et al., 1999). Thus, in parallel with the activation of mesocortical dopaminergic projections, re-inforcement of frontocortical adrenergic input by 5-HT$_{1A}$ autoreceptor agonists may improve cognition and, perhaps, mood.

Although there are currently no behavioral models permitting direct assessment of the potential control of negative symptoms, social withdrawal is a hallmark of deficit symptoms and, like clozapine, 5-HT$_{1A}$ autoreceptor agonists enhance active social interaction in rats (Corbett et al., 1993; Schreiber and De Vry, 1993). Furthermore, as outlined below, the positive influence of 5-HT$_{1A}$ autoreceptor agonists upon mood, and their attenuation of extrapyramidal (motor) side effects, should facilitate the control of negative symptoms.

There is extensive evidence in rodents suggestive of pro-cognitive properties of 5-HT$_{1A}$ receptor ligands in models of working, episodic, reference, and/or spatial memory, and concerning both acquisition and/or retention (Steckler and Saghal, 1995; Meneses, 1999). In certain paradigms, activation of 5-HT$_{1A}$ autoreceptors is involved (Carli et al., 1999; Menes-
subjects and there is evidence for antidepressive actions of
5-HT1A receptor agonists interacting with glutamatergic and/or
cholinergic transmission is implicated (Steckler and Saghal, 1995; Boast et al., 1999; Meneses, 1999). Thus, the inhibitory influence of postsynaptic 5-HT1A receptors upon pyramidal cells in the hippocampus interferes with their excitation by N-methyl-D-aspartate (NMDA) and muscarinic receptors (Steckler and Saghal, 1995; Meneses, 1999). Furthermore, 5-HT1A receptors may inhibit septohippocampal pathways, although data are inconsistent regarding hippocampal acetylcholine release (Steckler and Saghal, 1995). In any case, corticocortical and corticohippocampal glutamatergic pathways are enriched with inhibitory 5-HT1A receptors, the activation of which suppresses their activity (Francis et al., 1993; Boast et al., 1999). Notably, in this light, blockade of postsynaptic (and activation of presynaptic) 5-HT1A receptors alleviates cognitive deficits provoked by blockade of NMDA or muscarinic receptors (Boast et al., 1999; Carli et al., 1999). The relevance of cholinergic mechanisms to cognitive deficits in schizophrenia is unclear, but reduced activity at NMDA receptors may well contribute to perturbation of cognitive function in psychiatric patients (Breier, 1999; Meltzer et al., 1999). Very recently, the 5-HT1A partial agonist, tandospirone, was shown to improve verbal memory when administered in conjunction with haloperidol, providing clinical evidence that actions at 5-HT1A sites may ameliorate the treatment of cognitive symptoms (Sumiyoshi et al., 2000).

Relevance to Mood. 5-HT1A agonists express anxiolytic properties (Jann et al., 1990; Schreiber and De Vry, 1993) that may predominantly be ascribed to activation of 5-HT1A autoreceptors. Although early studies suggested that postsynaptic 5-HT1A sites likewise mediate anxiolytic actions, recent work indicates that their antagonism is associated with anxiogenic properties (Schreiber and De Vry, 1993). In view of the exacerbation of comorbid anxious states both by psychotic symptoms per se as well as by neuroleptic treatment, auxiliary anxiolytic properties would be advantageous for an antipsychotic agent. Anti-aggressive properties of 5-HT1A receptor agonists in experimental studies are likewise attributable to activation of 5-HT1A autoreceptors (Miczek et al., 1995). Because hostile behavior is often encountered in psychotic patients, such properties would also be beneficial. However, the relationship of serotonergic transmission to aggressive behavior remains ambiguous and rigorous demonstration of anti-aggressive actions of selective 5-HT1A ligands in man is awaited, so such potential advantages require cautious interpretation (Miczek et al., 1995).

Depressive states are increasingly recognized in psychotic subjects and there is evidence for antidepressive actions of 5-HT1A receptor agonists (Schreiber and De Vry, 1993). Although a role of postsynaptic sites has been postulated, this remains to be confirmed (Schreiber and De Vry, 1993; Millan et al., 2000), and 5-HT1A autoreceptors may be involved because their engagement reinforces mesocortical dopaminergic and adrenergic transmission (vide supra). Indeed while depressive and negative symptoms are distinct nosological entities of schizophrenia reflecting contrasting substrates, hypofrontality is also implicated in depressive states, and a common trait of mechanistically diverse antidepressant agents is an elevation in extracellular levels of DA and noradrenaline (NA) in FCX (Millan et al., 2000). Relevance to Extrapyramidal Side Effects. 5-HT1A receptor agonists attenuate induction of catalepsy by D2 receptor antagonists in rodents, a response predictive of extrapyramidal motor side effects (Wadenberg, 1996; Wadenberg et al., 1999). They also inhibit extrapyramidal motor effects of neuroleptics in primates (Casey, 1993). 5-HT1A receptors are virtually absent from the striatum, and these actions primarily reflect engagement of 5-HT1A autoreceptors localized in the MRN, although the DRN may also be implicated (Wadenberg, 1996; Wadenberg et al., 1999). Involvement of the latter would be consistent with projection of DRN-derived serotoninergic neurones to the striatum, raising the possibility that subsequent to a reduction of 5-HT release, postsynaptic mechanisms integrated therein abrogate cataleptogenic effects of striatal D2 receptor blockade. Modulation of nigrostriatal dopaminergic transmission is unlikely to be implicated, because 5-HT1A agonists exert a variable influence upon striatal DA release and fail to modify its enhancement by haloperidol (Millan et al., 1998a; Ichikawa and Meltzer, 1999, 2000). Nevertheless, other mechanisms may potentially be involved: e.g., actions in structures downstream of the striatum or modulation of corticostriatal glutamatergic afferents (Francis et al., 1993).

5-HT1A receptor agonists similarly inhibit induction of catalepsy by D2 receptor antagonists (Wadenberg, 1996) and by adenosine (A) agonists and inhibitors of nitric-oxide synthase, both of which inhibit striatal DA release (Mandhane et al., 1998; Nucci-da-Silva, 1999). Further underpinning the generality of their actions, 5-HT1A agonists suppress “inherited” catalepsy in genetically predisposed rats (Kulikov et al., 1994). Moreover, a further (extrapyramidal) behavioral response to haloperidol, vacuous chewing movements, is similarly inhibited by 5-HT1A receptor agonists (Espejo and Gil, 1997). Although the observations are clearly relevant to the acute motor perturbation (dyskinesias and dystonias) elicited by neuroleptics, it remains unclear whether activation of 5-HT1A (auto)receptors can prevent the emergence of tardive dyskinesia upon extended neuroleptic exposure; this debilitating and irreversible syndrome is unlikely to exclusively reflect interference with nigrostriatal dopaminergic transmission (Cunningham-Owens, 1996).

Apart from minimal extrapyramidal, motor side effects, a further characteristic of the “atypical” profile of clozapine is, in contrast to neuroleptics, a lack of hyperprolactinemia due to blockade of tonically active lactotrophic D2 receptors (Cunningham-Owens, 1996). However, actions at 5-HT1A receptors are unlikely to alleviate the elevation of circulating levels of prolactin triggered by hypophyseal D2 receptor blockade.

Actions of Clozapine at 5-HT1A Receptors

In light of the above comments, the demonstration that clozapine behaves as a partial agonist at human 5-HT1A receptors is clearly of significance (Assié et al., 1997; Newman-Tancredi et al., 1998), particularly because this action is expressed with a potency similar to that antagonizing D2 receptors. Indeed, several lines of experimental evidence sug-
gest that actions of clozapine at central 5-HT₁A sites participate in its functional actions.

First, much has (justifiably) been made of 1) the higher (100-fold) potency of clozapine at 5-HT₂A versus D₂ receptors, and 2) its superior potency at 5-HT₁A sites compared with haloperidol, whereas the opposite holds for D₂ receptors (Roth and Meltzer, 1995). However, clozapine is clinically used at doses substantially higher than those of haloperidol and at which significant D₂ receptor occupation is detected in PET imaging studies (Seeman and Tallerico, 1999; Kapur et al., 2000). If D₂ receptors are occupied then so, presumably, are 5-HT₁A sites for which it displays similar affinity. That clozapine genuinely occupies 5-HT₁A receptors at therapeutically effective doses was recently suggested by PET imaging studies in primates (Chuo et al., 2000), an approach which should be extended to the clinic.

Second, in experimental studies, many of the above-described actions of 5-HT₁A autoreceptor agonists have been observed with clozapine, which similarly activates and blocks pre- and postsynaptic 5-HT₁A receptors, respectively (Millan et al., 1998a,b; Newman-Tancredi et al., 1998). Notably, frontal-cortical (versus subcortical) release of DA and NA, enhancement of social interaction, anxiolytic and anti-aggressive properties, and attenuation of the cataleptogenic effects of neuroleptics (Corbett et al., 1993; Millan et al., 1998b; Ichikawa and Meltzer, 1999). Arguing by analogy, agonist actions of clozapine at 5-HT₁A autoreceptors may contribute to these effects. Correspondingly, they may contribute to the clinical improvement of negative symptoms and mood in the absence of extrapyramidal motor side effects. However, the “isolation” of a 5-HT₁A receptor-mediated component of action of clozapine is complicated by its other receptorial interactions. For example, apart from activation of 5-HT₁A autoreceptors, blockade of DRN-localized α₁-ARs contributes to suppression of serotonergic transmission by clozapine (Millan et al., 2000). Furthermore, blockade of postsynaptic 5-HT₂c receptors also participates in its acceleration of DA and NA release in FCX, as well as the expression of its anxiolytic properties (see Millan et al., 1998b, 2000).

The third line of evidence is, nevertheless, derived from interaction studies with WAY100,635 which neutralizes 5-HT₁A autoreceptor agonist properties of clozapine. Thus, in several but not all reports, WAY100,635 attenuated the increase in FCX levels of DA elicited by clozapine, as well as its anxiolytic properties and its ability to moderate the cataleptogenic actions of haloperidol (see Millan et al., 1998b; Ichikawa and Meltzer, 1999). This variable pattern of data reflects the above-mentioned implication of mechanisms other than 5-HT₁A autoreceptor stimulation in these effects of clozapine.

Clearly, further study is required to underpin the importance of 5-HT₁A receptors in the actions of clozapine. In this regard, the potential involvement of 5-HT₁A receptors in its influence upon cognitive-attentional function remains to be elucidated.

Other Antipsychotic Agents Interacting with 5-HT₁A Receptors

In light of the above, there is considerable interest in the potential role of 5-HT₁A receptors in the actions of antipsychotics (Roth and Meltzer, 1995; Ichikawa and Meltzer, 1999). Several drugs are illustrated in Fig. 3. Certain ones justify brief commentary.

First, like clozapine, ziprasidone shows equilibrated, but more potent, partial agonist and antagonist activity at 5-HT₁A and D₂ sites, respectively, in cellular models. However, the functional actions of ziprasidone at 5-HT₁A receptors in vivo are paradoxically weak relative to D₂ receptor blockade (Perry et al., 1998; Sprouse et al., 1999). Second, S16924 possesses a clozapine-like multireceptorial profile and shows pronounced partial agonist activity at 5-HT₁A receptors. Stimulation of 5-HT₁A autoreceptors plays a key role in its functional actions in experimental studies: notably, potentiation of mesocortical DA and NA release, anxiolytic properties, and blockade of haloperidol-induced catalepsy (Millan et al., 1998a,b). Third, clozapine, ziprasidone, S16924, and other antipsychotics shown in Fig. 3 display marked antagonist activity at α₁-ARs, 5-HT₂A, and/or 5-HT₂c receptors. On the other hand, the novel benzodioxane derivative, BTS79018 (Birch et al., 1999), may be distinguished by modest affinity for these sites. Experimental and clinical exploration of its functional profile should, thus, prove instructive in elucidating the significance of partial agonist properties at 5-HT₁A receptors for antipsychotic agents.

One “absentee” from Fig. 3 is the azaspironone and 5-HT₁A receptor agonist, buspirone, which possesses modest affinity at D₂ receptors and low affinity at α₁-ARs and 5-HT₂c sites. Buspirone, a clinically employed anxiolytic and antidepressant, was originally evaluated as a potential antipsychotic agent but yielded disappointing and inconsistent results in several small trials. In fact, it appeared to improve mood and reduce extrapyramidal motor symptoms in patients concurrently administered neuroleptics (Jann et al., 1990; see Sharma and Shapiro, 1996). However, the significance of these observations is difficult to discern because buspirone is rapidly degraded to 1-pyrimidinylpiperazine. This metabolite is virtually devoid of activity at the 5-HT₁A and D₂ receptors, although a potent antagonist at α₁-ARs, the blockade of which improves mood and motor function (see Millan et al., 2000). In addition, buspirone displays substantial efficacy at postsynaptic 5-HT₁A receptors (Schreiber and De Vry, 1993), whereas, as discussed above, low efficacy at these sites appears desirable for antipsychotic agents.

Optimal Efficacy and Potency at 5-HT₁A Receptors: A Crucial and Complex Question

As exemplified throughout this review, modest intrinsic activity permitting activation and blockade of pre- and postsynaptic 5-HT₁A receptors, respectively, appears to be the most appropriate profile for improved management of schizophrenia.

However, relative functional roles of pre- and postsynaptic 5-HT₁A receptors require clarification (Barnes and Sharp, 1999). Furthermore, drug efficacy at specific populations of the 5-HT₁A receptor in human brain in vivo depends critically upon a diversity of unknown variables, such as G-protein availability, receptor number and sensitivity, pre-exposure to 5-HT, and constitutive activity. Thus, it is virtually impossible to predict the precise actions of 5-HT₁A receptor ligands at specific populations of 5-HT₁A receptors.
in schizophrenia patients. This assertion is—unfortunately!—particularly valid for partial agonists. As a corollary of this uncertainty, it is difficult to ascertain the optimal degree of efficacy at 5-HT<sub>1A</sub> receptors required for potential antipsychotic agents. Yet this is a crucial factor since—at least upon initiation of treatment—excessive activation of postsynaptic 5-HT<sub>1A</sub> receptors may be deleterious (amnesic and anxiogenic actions, perturbation of sleep, and a constellation of physiological signs loosely termed the “syndrome”). On the contrary, a “pure” antagonist, in blocking postsynaptic sites, would exert procognitive properties, yet be deprived of potential advantages of autoreceptor stimulation. Indeed, 5-HT<sub>1A</sub> autoreceptor blockade may exacerbate extrapyramidal symptoms provoked by the D<sub>2</sub> receptor blockade (Prinssen et al., 1999).

In addition to efficacy, the relative potency of actions at 5-HT<sub>1A</sub> receptors versus D<sub>2</sub> receptor blockade is an incompletely resolved conundrum. That is, whether equilibrated affinity at 5-HT<sub>1A</sub> and D<sub>2</sub> sites is desirable or, alternatively, a clear preference in favor of the former. This will likely be a function of whether the drug interacts with other sites (“multireceptorial profile”) or exclusively recognizes 5-HT<sub>1A</sub> and D<sub>2</sub> receptors.

**Clinical Evaluation of Antipsychotics Interacting with 5-HT<sub>1A</sub> Receptors: Key Issues**

In concluding, it is appropriate to specify certain important considerations in the clinical evaluation of antipsychotic agents possessing marked activity at 5-HT<sub>1A</sub> receptors.

First, a crucial issue is the demonstration that, at doses exploited for efficacy studies, there is significant occupation of central 5-HT<sub>1A</sub> receptors. PET studies have proven indispensable for characterization of drug actions at 5-HT<sub>1A</sub> versus D<sub>2</sub> receptors and, with the availability of <sup>11C</sup>WAY100,635, this strategy may likewise be adopted for 5-HT<sub>1A</sub> receptors. This approach permits, further, observations of the relative occupancy of pre- versus postsynaptic sites, which may not necessarily be identical. Although PET imaging yields no information on drug efficacy, measures of core temperature, corticosterone, and growth hormone secretion may be of use (Roth and Meltzer, 1995). Drug influence upon such parameters can be extrapolated from experimental studies, although the relative contribution of pre- and postsynaptic 5-HT<sub>1A</sub> receptors to their modulation remains uncertain. Whether 5-HT<sub>1A</sub> receptor ligands gen-
ate an idiosyncratic electroencephalographic signature remains unclear, but their influence upon sleep patterns is well characterized, so such information would be important to acquire.

A second fundamental issue concerns patient selection and clinical assessment. It is improbable that actions at 5-HT$_{1A}$ receptors per se control positive symptoms in neuroleptic-responsive patients, although any potential improvement in resistant subjects patients justifies examination. Otherwise, therapeutic benefits are more likely to be encountered for deficit and cognitive symptoms. Their quantification should be a principal focus of studies adopting appropriate rating scales and, if feasible, models of cognitive-attentional function.

Third, activation of 5-HT$_{1A}$ autoreceptors is, in general terms, "activating" rather than sedative and/or motor-suppressant, so the introduction of antipsychotics possessing such actions in patients accustomed to neuroleptics (and tranquillizing agents) should be undertaken cautiously, in such actions in patients accustomed to neuroleptics (and tranquillizing agents) should be undertaken cautiously, in particular, if concurrent D$_2$ receptor blockade cannot be guaranteed. In this light, for an optimal appreciation of the potential benefits and disadvantages of agents interacting with 5-HT$_{1A}$ receptors, if possible, it would be advisable to avoid recent or simultaneous utilization of other classes of psychotropic agent.

Finally, because 5-HT$_{1A}$ receptors modulate sympathetic outflow, the potential modification of cardiovascular parameters, particularly in association with a$_1$-AR and 5-HT$_2$ receptor blockade, requires careful surveillance.

Such potential complications are arguably inherent to any drug class possessing a novel mechanism of action. Furthermore, these issues are more relevant at the onset of treatment and do not appear unsurmountable within the framework of prudent and appropriately designed, long-term clinical trials.

Conclusions

In conclusion, selective 5-HT$_{1A}$ receptor ligands are unlikely to be of use in the treatment of schizophrenia. Nevertheless, antipsychotics possessing partial agonist properties at 5-HT$_{1A}$ receptors (allowing stimulation and antagonism of pre- and postsynaptic populations, respectively) may offer advantages. In this respect, both dual 5-HT$_{1A}$/D$_2$ receptor and multireceptorial ligands are of interest. Additional study is necessary to define the precise degree of potency and efficacy at 5-HT$_{1A}$ receptors requisite for optimization of clinical benefit. Antipsychotics interacting with 5-HT$_{1A}$ receptors are unlikely to provide a panacea for the problem-free treatment of all schizophrenic patients, and well designed, thorough, and imaginative clinical trials are required to more precisely characterize the potential use of this mechanism of action in the management of psychotic disorders.

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