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Dopamine Neurotransmission and Atypical Antipsychotics in Prefrontal Cortex: A Critical Review

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Abstract

Schizophrenia has been historically characterized by the presence of positive symptomatology, however decades of research highlight the importance of cognitive deficits in this disorder. At present, cognitive impairments remain one of the most important unmet therapeutic needs in schizophrenia. The prefrontal cortex (PFC) controls a large number of higher brain functions altered in a variety of psychiatric disorders, including schizophrenia. Histological studies indicate the presence of a large proportion of PFC neurons expressing monoaminergic receptors sensitive to the action of current atypical antipsychotics. Functional studies also show that these medications act at PFC level to increase dopamine neurotransmission in the mesocortical pathway. Here we focus on monoaminergic molecular targets that are actively being explored as potential therapeutic agents in the basic and clinical cognitive neuroscience research, to support the development of co-treatments used in conjunction with antipsychotic medications. These targets include dopamine and serotonin receptors in the prefrontal cortex, as well as elements of the noradrenergic system.

Keywords

Antipsychotic drugs – cognitive deficits – monoamines – prefrontal cortex – schizophrenia

1. INTRODUCTION

The antipsychotic drugs (APDs) are effective for treating the psychotic symptoms of mental conditions such as schizophrenia, bipolar disorder and major depression and also, can be used for the treatment of psychotic symptoms of dementia. The serendipitous discovery of chlorpromazine (classical or typical antipsychotic) in the early 1950s and development of clozapine (first atypical antipsychotic) in the late 1960s represent two major millstones in the pharmacotherapy of schizophrenia [**1,2**]. During the past half century, numerous first-, second-, and third generation antipsychotics were developed and dramatic growth of research in the area of pharmacological treatment of schizophrenia has advanced our understanding of the neurobiology and neuropharmacology of the illness [**3,4**]. Indeed, pharmacotherapy for schizophrenia is highly effective but at the same time there is tremendous unmet clinical need.

The mechanism of action of APDs is based on the hypothesis that the schizophrenia involves a dysregulation of dopaminergic circuit in the brain with excess dopaminergic activity in the mesolimbic pathway and reduced dopaminergic signaling in the mesocortical pathway [**5-9**]. Based on this model, currently available antipsychotic drugs block to a different extent the dopamine (DA) D2-like receptors (D_2, D_3 and D_4 subtypes) in the brain. Thus, the blockade of these receptors in the mesolimbic dopaminergic pathway is thought to account for the therapeutic properties of classical antipsychotics (first generation) like haloperidol **(Table 1).** However, the antagonism of the same receptors in other brain dopaminergic pathways,

such as the nigrostriatal system -involved in the motor behavior- or the tubero-infundibular pathway -involved with the hypothalamic hormonal secretion- results in important side effect that limit the effectiveness of classical APDs, reducing compliance and making some patients to abandon the treatment once psychotic symptoms have remitted. Moreover, the blockade of DA actions in the prefrontal cortex (PFC) is detrimental for cognitive function, which does not help to improve the negative symptoms and cognitive deficits in schizophrenia [**10,11**]. On the contrary, the administration of DA D2-blocking agents induces negative symptoms in healthy individuals [**12**].

Unlike classical antipsychotics, the so-called atypical antipsychotics (second generation) with clozapine as prototype inhibit the actions of DA at D2-like receptors to a much lower extent **(Table 1)**. Therefore, they do not produce the motor and hormonal side effects of classical compounds. Moreover, clozapine is found to be superior that classical antipsychotics, particularly for the treatment of negative symptoms (poverty of thought, blunted affect, social withdrawal, etc.) and cognitive impairment of the disease [**11**,**13,14**]. However, this classification criterion has become somewhat imprecise in view of several new antipsychotics (third generation, e.g. aripiprazole) with pharmacological profiles comparable to that of classical antipsychotics (preferential affinity for D2-like receptors) and clinical profiles similar to that of atypical antipsychotics (improvement of positive and negative symptoms and low extrapyramidal risk) [**1,15**].

The action of atypical APDs takes place predominantly through the blockade of serotonergic receptors (5-HT_{2A}R and 5-HT_{2C}R) for which they display a higher *in vitro* affinity [**16**], although the direct or indirect 5-HT_{1A}R agonism plays a key role in their mechanism of action (see below). *In vivo* neuroimaging studies using PET (positron emission tomography) scan or SPECT (single photon emission computed tomography) have confirmed that therapeutic doses of atypical APDs produce a much greater occupancy of 5-HT_2 than of DA D2 receptors [**17**]. Neuroimaging studies have also revealed that there was a wide variation in D2-like receptor occupancy among patients on the same dose of antipsychotic and within the same individual in different stages (first episode vs. chronic) and phases (relapse vs. remission) of the illness [**17**]. Classical APDs are clinically effective at doses that result in a 70-75% occupancy of DA D2 receptors, at which motor side effects emerge. However, D2-like receptor occupancy with atypical APDs never reaches this threshold -except for risperidone-, which explains the favorable profile of atypical compounds on motor side effects – yet they show important metabolic side effects- [**18-20**].

It remains unclear how atypical APDs can exert their therapeutic action with sub-threshold occupancy of DA D2-like receptor indicating that D2 receptor blockade alone cannot explain the therapeutic efficacy. Although the 5-HT_{2A}/D2 affinity ratio is considered the main criterion to define the “atypicality” of antipsychotics [**16**], there are discrepant views that focus on the way that these drugs interact with DA D2 receptors [**21**]. In fact, Kapur and Seeman [**21**], proposed that low affinity for and fast dissociation from

D2 receptors may be the critical property for “atypicality”. Moreover, a recently marketed drug (aripiprazole) shows high affinity for DA D2 receptors and displays supra-threshold occupancy but does not produce extrapyramidal side effects, due to its partial agonist character at D2 receptors (contrary to the classical antipsychotics, which are antagonists at this receptor) [**22-25**]. Therefore, a variety of pharmacological mechanisms seem to account for both the therapeutic and undesirable effects of antipsychotic drugs [**26**] **(Fig. 1)**.

The limited effectiveness of the classical and atypical APDs on negative/affective symptoms and cognitive deficits in schizophrenia indicates that there is ample room for improving the therapeutic action of antipsychotics. Furthermore, in a substantial number of patients, positive/psychotic symptoms are resistant to currently available medications [**27**]. Consequently, there is an urgent need for more effective and better-tolerated antipsychotic agents, and to develop mechanistically new compounds that possess pharmacological activity for novel targets which address the various symptom dimensions of schizophrenia.

2. COGNITIVE DEFICITS IN SCHIZOPHRENIA

Cognitive impairments represent a core deficit in the schizophrenia [**28**]. These have been associated with disorganization and negative symptoms as well as with poor functional outcomes [**29-31**]. Likewise, cognitive dysfunction shows only modest improvement with approved available

therapies and the vast majority of patients treated with the second and third generation APDs continue to experience significant cognitive disability [**32,33**].

Hagan and Jones [**34**] carried out a survey of the literature describing the effects of APDs upon cognition in schizophrenia and, concluded that there is some support to the hypothesis that atypical APDs can improve negative and cognitive symptoms in schizophrenia across a number of domains. Recently, academic and industry initiatives (e.g. MATRICS- Measurement and Treatment to Improve Cognition in Schizophrenia) identified seven primary cognitive domains: working memory, speed of processing, verbal learning, attention and vigilance, reasoning and problem solving, visual learning and social cognition that are crucial for developing targets for the treatment of schizophrenia [**35**]. However at the present, the understanding of which cognitive domains are affected by which compound is poor [**36**]. The relationship between antipsychotic drug and cognitive function is further complicated by the fact that many drug studies are associated with a specific cognitive measures rather than cognitive domains [**34,36**]. Indeed, the current medications are accurately described as “antipsychotic” rather than “anti-schizophrenia” drugs. Thus, in response to the increased awareness of the clinical importance of impaired cognition in schizophrenia, there is a dramatic increase in research directed toward understanding the pathophysiological mechanisms underlying these deficits as well as developing more effective therapies -either as mono-therapy or as adjunctive treatments added to currently APDs- for this aspect of the illness.

2.1 Role of the Prefrontal Cortex

The adequate engagement of cognitive control requires the coordination of multiple brain regions including the prefrontal cortex (PFC). The PFC is the most rostral part of the frontal lobe and has poorly defined anatomical boundaries. However, in all examined mammalian brains, it is described by its reciprocal connectivity with the mediodorsal (MD) nucleus of the thalamus. In the human brain, the PFC includes Broadman areas 8–14, 24–25 and 44–47 and contains three major regions: orbital, medial (including the anterior cingulated cortex) and dorsolateral cortex (DLPFC). This cortical area is involved in many brain functions, such as perception, attention, memory, language, consciousness, affect, etc. The PFC in higher primates (including humans) is particularly important for working memory, which is a cognitive buffer that allows an organism to maintain a representation based on recent sensory information and uses it to plan future behavior [**37-40**]. Orbital and medial regions of the PFC are mainly associated with the emotional behavior whereas DLPFC region is involved in the cognitive control. Hence, functional neuroimaging studies in healthy individuals have shown activation of a specific cortical network in the DLPFC and anterior cingulated cortex during tasks requiring cognitive control [**41-44**]. When such prefrontal brain regions are damaged, affected individuals show predictable deficits in the context and response inhibition [**39**].

Early studies of PFC structure and function in non-human primates [**45-47**] suggested that the PFC serves as a temporary storage for incoming

information, maintaining it “online” for immediate use. However, more recent works indicate that the role of PFC is much more complex. Thus, the PFC receives sensory information from the external world, stored emotional and contextual information from limbic and temporal areas, and has a large number of intrinsic connections between different sub-regions of the PFC itself. On the other hand, it projects to cortical premotor and motor areas and to the basal ganglia, which allows to performing motor acts once a particular behavior has been selected. This connectivity confers to the highest integrate level of all cortical areas and enables it to exert a top-down processing to coordinate the behavior [**39,40**]. Although a complete discussion of this literature is beyond the scope of this review, it is known that monoaminergic neurotransmitters, such as dopamine (DA), norepinephrine (NE) and serotonin (5-HT) modulate the PFC function [**48-56**] (see below: Monoaminergic Innervation of the Prefrontal Cortex). In particular, extensive research has associated the cognitive symptoms with a dopaminergic dysregulation in the PFC [**52-54,57**]. DA neurotransmitter has been linked to a wide variety of functions including motivation, reward, affect and movement; all of which could affect performance on cognitive tasks [**52, 58-63**]. Previous works in non-human primates have shown an inverted U relationship between cognitive performance in spatial working memory tasks with the occupancy of DA D_1 receptors [**52,64,65**]. Thus, a very low or excessive dopaminergic activity (as that produced by stress [**66**]), results in a poor cognitive function.

Schizophrenia is associated with many dysfunctions -anatomical, cellular, neurochemical and neuronal circuits- in the PFC and subcortical regions. Post-morten and neuroimaging studies have revealed the existence of a reduced PFC volume, decreased cortical layer thickness, tight packing of pyramidal neurons and diminished neuropil in the brains of the patients [**8**,**67,68**]. Alterations in key neurotransmitters such as glutamate, γ-aminobutyric acid (GABA) and DA and its receptors have also been reported [**8**,**69-72**]. Moreover untreated patients show a reduced energy metabolism in the PFC which has been related with negative symptoms [**73,74**]. However, psychotic episodes are linked with hyperactivity of various cortical areas including the PFC [**75,76**] and an abnormal hyperdopaminergic state in the mesolimbic pathways, among other neurotransmitter systems [see ref. **77,78** for review].

Although cognitive deficits observed in schizophrenia have long been attributed to reduced activation of the dorsolateral PFC (known as hypo-frontality), many cortical and subcortical structures are also affected, with a complex pattern of region-dependent hypo- or hyperactivation [**79-82**]. The increased activity may reflect an attempt to compensate for insufficient performance. For instance, a disturbance of fronto-cortical–striatal–thalamic loops, together with impaired top-down cognitive control from the cortex, contributes to deficits in attention, working memory and executive function [**83-85**]. Indeed, PET studies with fluorine 18-labled fluorodopa focused on frontal and striatal functions in a clinical high risk patients revealed that the degree of attenuation of DLPFC activation was associated with the severity

of striatal DA dysfunction illustrated by the elevated Ki value [**86,87**]. Furthermore, impaired verbal learning and language in schizophrenia can be related to lower connectivity between the temporal–parietal zone (Wernicke's area) and frontal lobes, as well as reduced left hemisphere lateralization of Broca's area and functionally related regions [**88**].

Moreover, the PFC is also connected with the hippocampus and the mediodorsal nucleus of the thalamus, two of the areas showing anatomical and/or functional alterations in schizophrenia [**89,90**]. Given the connectivity between these areas, a genetic- and/or environment-induced pathological change in one of them may result in downstream changes in other structures of the network and in an overall alteration of its function. Alternatively, pathological changes may simultaneously occur in several brain areas contributing independently to the emergence of schizophrenia symptoms.

2.2 Monoaminergic Innervation of the Prefrontal Cortex

The brainstem monoaminergic systems (ventral tegmental area – VTA/ DA neurons; *locus coeruleus* – LC/ NE neurons and raphe nuclei – RN/ 5-HT neurons) are reciprocally connected with the PFC and modulate the activity of memory networks and animal behavior [**48-56**, **65, 91-95**]. In a very simple view of brain function, it could be stated that the neurotransmitters glutamate and GABA are necessary for the *life* of the brain, whereas monoamines are necessary for the *quality of the life*. Not surprisingly most pharmacological treatments for neuropsychiatric disorders

are directed towards monoaminergic systems that exert a fine tuning of cortical neuronal function **(Fig. 2)**.

The cellular basis for DA actions in the PFC have been extensively investigated, and a plethora of studies have examined the effect of DA or selective D_1 and D_2 receptor agonists on the activity of pyramidal and GABAergic neurons in the PFC of rodents and nonhuman primates [**96-98**]. However, despite an extensive research, there is not a unified view of DA actions in the PFC, and many of these studies have yielded non-convergent and often contradictory conclusions [for review see **99,100**]. Recently, Santana et al., [**101**] showed that both D_1 and D_2 receptor messenger RNAs (mRNAs) are expressed in PFC pyramidal and GABAergic neurons of rat using double *in situ* hybridization **(Fig. 3)**. The proportion of pyramidal and GABA cells expressing these transcripts showed great regional variability in the PFC with little overlap, except for layer V contains a similar percentage of cells expressing one or other receptor transcript, adding a further element of complexity. One interesting view is that DA D_1 receptor activation increases the time in depolarized ('up') states of pyramidal neurons in PFC whereas DA D_2 receptor activation may decrease firing probability [**98**]. Given the differential expression of D_1 and D_2 receptors in various cortical layers, this effect is likely to take place only in layer V of the PFC, where a substantial proportion (20-25%) of pyramidal cells may express both receptors [**101**] **(Table 2).** In this way, DA innervations of the PFC may act as a filter, enabling only high intensity inputs to trigger action potential in PFC neurons [**98**].

Unlike DA, the study of the actions of NE on PFC neurons has received a comparatively lower attention, despite several adrenergic receptors are present in the PFC. Of these, alpha$_1$-adrenoceptors (α_{1A}, α_{1B}, and α_{1D} subtypes) show a remarkable high density in various layers of the PFC [**102-104**]. Indeed, alpha$_1$-adrenoceptors are expressed by a high proportion of pyramidal (59-85%) and GABAergic (52-79%) neurons in rat PFC [Santana et al., IntJNP submitted for publication] **(Table 2)**. It has been described that alpha$_1$-adrenoceptors mediate the excitatory actions of NE on pyramidal neurons of medial PFC through the activation of phospolipase C, which results in IP3 production and mobilization of Ca^{2+} stores [**105,106**]. Rats and monkeys exposed to uncontrollable stress exhibit prominent deficits in working memory abilities related to NE stimulation of alpha$_1$-adrenoceptors [**107**]. In addition, the blockade of them in the PFC has little effect on working memory under non-stress conditions [**108,109**], but protects this function during stress [**95,110**]. On the other hand, moderately elevated NE levels, acting on cortical alpha$_{2A}$-adrenoceptors improve the cognitive performance. Thus, it has been described that alpha$_2$-adrenergic agonists such as clonidine and guanfacine enhance the delayed response performance in monkey and rats, at least in part, helping to protect memory from irrelevant stimulation [**111,112**].

The PFC is also innervated by prominent serotonergic projections from the raphe nuclei [**113**] and expresses several 5-HT receptor subtypes, with a particularly high density of 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors [**114-117**] **(Fig. 3)**. 5-HT$_{2C}$ receptors are also located with a moderate density in the PFC

[**117,118**]. Histological studies using immunohistochemistry and *in situ* hybridization have revealed the presence of 5-HT_{1A} and 5-HT_{2A} receptors in a large proportion of pyramidal and GABAergic neurons in the PFC of rodent and monkeys [**119-125**] (**Table 2**). 5-HT_{1A} and 5-HT_{2A} receptors mediate, respectively, the direct hyperpolarizing and depolarizing actions of 5-HT and selective agonists on PFC pyramidal neurons, as assessed *in vitro* and *in vivo* [see ref. **125** for review]. Also, 5-HT can inhibit pyramidal neurons through the activation of 5-HT_{2A} and 5-HT_3 receptors in GABAergic interneurons mainly located in superficial cortical layers [**126**]. In contrast, selective 5-HT_{1A} agonists also activate pyramidal neurons via the stimulation of 5-HT_{1A} receptors expressed on GABAergic neurons **[127-129]**. Hence, 5-HT may influence the descending excitatory input into subcortical areas as well as midbrain serotonergic nuclei through the direct and indirect modulation of the activity of pyramidal neurons in PFC (**Fig. 2**).

However, despite the greater proportion of PFC neurons expressing serotonergic *vs.* dopaminergic receptors, the exact role of serotonergic function in PFC is poorly known, compared to that of dopaminergic transmission. To understand the cellular and network basis of monoamine action in PFC, we have performed a number of double *in situ* hybridization studies to examine the expression and distribution of some monoaminergic receptor in the rat PFC (**Table 2**). Notably, functional studies have been indicated that 5-HT depletion in the orbital prefrontal cortex (OFC) of primates reduces cognitive flexibility (i.e. animals have a reduced capacity to learn changing rules) [**130**]. Similarly, healthy volunteers who received a

tryptophan-depleting drink –in order to reduce brain 5-HT synthesis- showed a decreased performance of reversal learning in the PFC [**131**]. Also, blockade of 5-HT_{2A} receptors in the dorsolateral PFC antagonizes the persistent neuronal activity during a working memory task in monkeys [**132**]. On the other hand, an excessive activation of cortical 5-HT_{2A} receptors by agonists such as lysergic acid (LSD) or 1-(2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI) likely underlies the hallucinogenic properties of these compounds, which include not only perceptual but also cognitive and mood alterations [**133**].

3. MOLECULAR TARGETS FOR POTENTIAL DRUG DEVELOPMENT STRATEGIES AIMED AT ENHANCING COGNITION IN SCHIZOPHRENIA

A better understanding of the cognitive dysfunction in schizophrenia is critical for future drug discovery. As described in section 2, schizophrenia is associated with many anatomical, cellular and neurochemical alterations as well as dysfunctions in several brain circuits. Previously, different hypotheses have been proposed to integrate the neurochemical changes observed in schizophrenia. They include the classical dopaminergic hypothesis, glutamate or NMDA receptor hypofunction, serotonin system, and GABAergic hypofunction [**70-72,134,135**]. More recently, a neuronal circuitry model of glutamate-GABA-dopamine interactions and the effects upon working memory and cognition in the PFC has been considered to obtain a more coherent understanding of the cognitive impairments in schizophrenia [**70,71,136,137**]. Thus, a comprehensive approach

underlying neuropathology will facilitate the development of better treatments targeted at cognition. The primary molecular targets identified for treating cognitive dysfunction included nicotinic and muscarinic acetylcholine receptors, the glutamatergic excitatory synapse, GABAergic system, and monominergic receptors mainly in the PFC. Below we review the current drugs which act on monoaminergic receptors and/or exciting ongoing approaches to selectively enhance the DA neurotransmission in the mesocortical pathway. These pharmacological strategies underscore the potential therapeutic value of the adjunctive cognitive-enhancing agents in combination with APDs for the treatment of impaired cognition, both generally and specifically in schizophrenia.

3.1 Dopaminergic Targets

3.1.1 D_1 Receptors

As mentioned above, DA D_1 receptors play an important role in cognitive function such as working memory. It is hypothesized that either decrease or excessive D_1 receptor stimulation is deleterious to PFC cognitive function; therefore, an “optimal” level of receptor activation is necessary for normal cognitive function [**52,65**]. Earlier preclinical studies demonstrate that the selective D1-like antagonists are active in most conventional rodent models predictive of antipsychotic-like activity [**138,139**]. However, clinical trials of the selective D_1 antagonist SCH39166 [**140,141**] and NNC 01-0687 [**142**] failed to demonstrate antipsychotic properties. On the other hand, selective full D_1-like receptor agonists, such as dihydrexidine (DAR-0100), A77636

and SKF81297, have been reported to have cognitive-enhancing actions in rodents and non-human primates [**143-145**]. In a pilot study, a single dose of dihydrexidine was well tolerated in patients with schizophrenia, but did not produce delayed clinical or neuropsychological improvements [**146**]. However, it induced a significant increase in prefrontal brain activity compared with placebo, suggesting that this drug and other full D1-like receptor agonists may be able to modulate prefrontal dopaminergic function in schizophrenia.

3.1.2 D_2 Receptors

The idea of using D_2 receptor partial agonists was initially proposed by Arvid Carlsson in the early 80s (reviewed in Carlsson et al., [**71**]). However, several clinical studies with D2-like receptor partial agonists, including talipexole, preclamol, roxindole and pramipexole, failed to demonstrate a clear therapeutic effect on positive symptoms of schizophrenia, although the results suggested possible beneficial activity against negative symptoms [**147,148**]. In fact, aripiprazole (OPC-14597) developed along the same lines, has reached therapeutic success. This compound is distinct from all other known APD drugs by virtue of its partial agonist effect at a number of G-protein coupled receptors including DA D2-like as well as serotonin 5-HT_{1A} receptors. In contrast, it has an antagonist action at 5-$HT_{2A/2C}$ receptors [**24,25**]. Concerning to the dopaminergic pathways, preclinical studies indicate that aripiprazole induced a very moderate reduction of DA neuron activity and a decreased striatal DA release [**149,150**], while

increased the PFC DA neurotransmission by the activation of 5-HT_{1A}R [**150**]. Similarly, cariprazine (RGH-188), a novel putative APD, is currently in phase III of clinical trials. It exhibits partial agonism at D_2/D_3 receptors, with preferential binding to D_3 receptors, and partial agonism at 5-HT_{1A}R [**151,152**]. Cariprazine displayed a similar intrinsic activity at D_2/D_3 receptors but higher potency than those of aripiprazole. Preclinical studies have suggested that its propensity for extrapyramidal symptoms is low and that it may have pro-cognitive properties [**152**]. Furthermore, OPC-34712 is a novel D_2 partial agonist with an enhanced affinity for 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptors (Otsuka Pharmaceutical Co., Ltd.). It is in phase III testing for schizophrenia.

3.1.3 D_3 Receptors

All antipsychotic drugs, irrespective of their overall receptor binding profiles, affect the brain DA transmission. DA exerts its actions via five different receptors (D1-like and D2-like receptors including D_1 and D_5 and, D_2, D_3 and D_4 subtypes, respectively) offering a broad palette of targets for the conception of novel antipsychotic agents. Based on the atypical features of several drugs with predominant actions at DA D_2/D_3 receptors including amisulpride, remoxipride and sulpride, an only D_2/D_3 profile had been proposed for atypical APD actions and it represents a promising target for enhancing cognition [**26,153,154**]. Experimental studies suggest that antipsychotic drugs which preferentially block presynaptic D_3 receptors lead to an enhanced DA release from dopaminergic terminals, whereas the

concurrent blockade of the same postsynaptic receptors in cortical and limbic structures may improve negative symptoms and cognitive deficits [**153**].

In this regard, selective D_3 antagonists have been developed (S33084, S33138, SB-277011-A, AVE5997) [**155-157**], but there are limited animal behavioral data at this time. In a preliminary study, (+)-UH232, a D_3 antagonist, actually worsened psychotic symptoms in drug-free patients with schizophrenia [**158**]. In a recent 6-week double-blind study, a selective D_3 antagonist ABT-925, used as monotherapy, failed to demonstrate any significant benefits for psychiatric symptoms in patients with acute schizophrenia [**159**].

3.1.4 D_4 Receptors

D_4 receptors are present on both pyramidal neurons and GABA interneurons in the PFC and hippocampus, brain areas important for cognitive function [**160**]. The high affinity of clozapine and the anatomical distribution of the D_4 receptor were features that made it a potential target in the development of novel antipsychotic medications. However, negative studies for the highly selective D_4 antagonist L-745,870 [**161**], the 5-HT_{2A}/D_4 antagonist finanserin [**162**] and sonepiprazole [**163**] suggest that the selective D_4 receptor antagonist mechanism is ineffective, at least as monotherapy.

Contradictory evidence also suggests that D_4 receptor agonists may improve cognitive function. For example, the selective D_4 agonist A-412997

showed dose-dependent improvement in social recognition in rats, a model of short-term memory [**164**] and the D_4 agonist PD168077 was shown to facilitate memory consolidation of an inhibitory avoidance learned response in mice [**165**]. These effects have been hypothesized to be due to D_4 receptor modulation of inhibitory GABAergic signaling in the PFC and thereby, indirectly enhance cortical excitability.

3.2 Serotonergic Targets

3.2.1 5-HT_{1A} Receptors

Among the various G-protein monoaminergic receptors, there is growing interest in postsynaptic 5-HT_{1A} receptors as potential targets for antipsychotic drug action [**166**]. This receptor seems to contribute to the ability of atypical (but not classical) APDs to increases cortical DA neurotransmission, an effect involved in the improvement of negative symptoms and cognitive dysfunctions in schizophrenia [**127,150,167-169**]. Of the current atypical drugs, only two: aripiprazole and ziprasidone, are partial 5-HT_{1A} receptor agonists [**23,171,172**] **(Table 1).** Moreover, clozapine occupies *in vivo* 5-HT_{1A} receptors in primate brain at clinically representative plasma levels despite it shows a negligible in vitro affinity for these receptors [**173**]. However, a similar study made in human has given negative results [**174**] and hence, it is still controversial whether clozapine behaves as a 5-HT_{1A} agonist *in vivo*.

Interestingly, preclinical studies indicated that several atypical APDs including risperidone, olanzapine, clozapine, ziprasidone and aripiprazole

(with markedly different *in vitro* affinities for 5-HT_{1A} receptors) increase DA release in the medial PFC of rodents by a local 5-HT_{1A} receptor-dependent mechanism [**127,150,170,175**]. Further, 5-HT_{1A} receptors are up-regulated in postmortem PFC in schizophrenia, suggesting a deficit in 5-HT_{1A} function [**176,177**]. Likewise, the 5-HT_{1A} partial agonists, tandospirone and buspirone, can enhance certain domains of cognition in patients receiving typical or atypical APDs [**178,179**]. Based on these data, compounds that possess 5-HT_{1A} agonism combined with D2-like receptor antagonism, including SLV-313, SSR-181507, F-15063, S-16924, BSF 190555 (BTS 79018) and RGH-188, are being developed as potential APDs [**180,181**]. It is suggested that the balance between D2-like receptor antagonism and 5-HT_{1A} receptor agonism may be critical in determining the superior efficacy of these compounds. Of particular interest is the development of drugs showing preferential activity at postsynaptic 5-HT_{1A} receptors, such as F15599 [**182**], which are effective alone in animal models of schizophrenia and cognition [**183**].

3.2.2 5-HT_{2A} Receptors

As previously described, 5-HT_{2A} receptors are particularly abundant in the pyramidal neurons from cortical layer V [**123**], where they have been shown to colocalize with NMDA glutamate receptors [**184**] suggesting a role in modulating cognitive functions. In addition, it is likely that a prominent role of 5-HT_{2A} receptors in antipsychotic action is to contribute to stabilizing dopaminergic tone, particularly along to mesocortical pathway [**185,186**].

Interestingly, preclinical studies indicated that PFC 5-HT_{2A} receptor stimulation increases the activity of VTA dopaminergic neurons as well as the DA release in medial PFC and VTA [**187,188**], and the selective 5-HT_{2A} antagonist M-100907 reverses these effects [**188**]. These results suggest that the atypical APDs by antagonism at the cortical 5-HT_{2A} receptors may decrease the stimulated dopaminergic activity, a mechanism by which these drugs could exert their therapeutic effect. The observation that PFC pyramidal neurons projecting to the VTA express 5-HT_{2A} receptors provides an anatomical support to the above observations [**189**].

Clinical trials have demonstrated that addition of ritanserin, a relatively selective 5-$HT_{2A/2C}$ antagonist, to a typical APD produced significant reductions in negative symptoms and depressed mood in chronic schizophrenia [**190,191**]. Moreover, ritanserin potentiated the clinical efficacy of risperidone on negative symptoms [**192**]. However, the selective 5-HT_{2A} antagonist M-100907 was discontinued after two phase III clinical trials demonstrated lower antipsychotic efficacy compared with haloperidol [**193**]. A phase II trial of the 5-$HT_{2A/2C}$ antagonist SR-46349B also demonstrated efficacy superior to placebo but inferior to haloperidol [**193**]. Since nearly all approved atypical APDs have potent 5-HT_{2A} antagonist properties, it is unlikely that adding on a drug with potent 5-HT_{2A} antagonism will provide any significant improvement of cognition in patients with schizophrenia.

It has been recently recognized that many atypical APDs are inverse agonist at the 5-HT_{2A} receptor rather than antagonists [**194**]. In contrast to

antagonist, inverse agonists lack negative intrinsic efficacy and can attenuate basal constitutive signaling activity and block only agonist-induced responses. Pimavanserin tartrate (ACP-103) is the first 5-HT_{2A} inverse agonist to enter clinical trials as a treatment for schizophrenia. In phase II, this drug seemed to be safe, and potentiated the therapeutic effects of risperidone [**195**]. In preclinical studies, ACP-103 potentiates haloperidol-induced DA neurotransmission in mesocortical and mesolimbic pathways [**196**].

3.2.3 5-HT_{2C} Receptors

Many drugs that bind to 5-HT_{2A} receptors with high affinity also bind to some extent to the structurally related HT_{2C} receptor. This receptor has received relatively little attention in psychopharmacology. This may be partly due to the inadequacy of specific techniques (e.g. radioligand binding and immunocytochemistry) to determine the regional and cellular expression of 5-HT_{2C} receptors in brain tissue. However evidence from a variety of sources has implicated this receptor in several important physiological and psychological processes including motor function, anxiety, feeding behavior and appetite. In addition, some interesting pharmacogenetic observations have focused on the potential importance of this receptor in several aspects of atypical APD actions [**197-199**].

The 5-HT_{2C} receptor possesses a unique ability to tonically regulate DA release [**200**] and plays a critical role in mediating the interaction between serotonergic and dopaminergic systems [**201-203]**. Thus, agonists of this

receptor may inhibit the DA release in the mesolimbic pathways [**204**], while the systemic administration of 5-HT_{2C} receptor antagonist SB242084 increased DA release in the nucleus accumbens and in the PFC [**203**]. Further, the selective 5-HT_{2C} receptor agonist CP-809,101 was active in the novel object recognition, an animal model of cognitive function [**205**]. However, there is a concern that 5-HT_{2C} receptor agonists may cause motor alterations by reducing dopaminergic transmission in the mesocortical and nigrostriatal pathways [**206**], while 5-HT_{2C} receptor antagonists may mediate some of the undesirable effects of atypical antipsychotics such as weight gain [**197-199**].

3.2.4 5-HT_3 Receptors

The 5-HT_3 receptors are mainly expressed in cortical and hippocampal GABAergic interneurons [**126**]. The stimulation of them by endogenous 5-HT provokes an inhibition of the pyramidal glutamatergic neuron activity [**126**]. 5-HT_3 receptors are involved in the release of several neurotransmitters, including acetylcholine (Ach) and DA [**207,208**]. In preclinical models, 5-HT_3 antagonists have been shown to have a broad spectrum of psychotropic effects, including correcting psychotic-like behavior, improving cognitive deficits and antagonizing locomotor hyperactivity induced by DA stimulants [**209**]. Adjunctive treatment with ondansetron, a highly selective 5-HT_3 antagonist, was shown to be effective for negative symptoms and cognitive impairments (visual memory) in patients with chronic schizophrenia on stable antipsychotic therapy [**210-**

212]. However, a replication with larger sample sizes will be necessary before endorsing a role for adjunctive ondansetron in schizophrenia**.**

3.2.5 5-HT$_4$ Receptors

Serotonin 5-HT$_4$ receptors are found at high densities in the hippocampus, frontal cortex and amygdala, suggesting a role of these receptors in cognitive functions [**213**]. Indeed, 5-HT$_4$ receptors have been shown to be markedly decreased in patients with Alzheimer's disease [**214**]. In addition, 5-HT$_4$ agonists have been promise in the treatment of cognitive impairments by enhancing cholinergic transmission in the hippocampus and also, modulate the DA, GABA and 5-HT release. 5-HT$_4$ receptor agonists such as BIMU1, RS67333, RS17017 were shown to enhance memory in several animal models [**215**]. The combined administration of partial 5-HT$_4$ receptor agonists (for example, RS67333, SL65.0155) with cholinesterase inhibitors may enhance cognition to a greater extent than either treatment alone [**216,217**]. Although there have been no clinical trials of 5-HT$_4$ receptor agonists as add-on therapy in patients with schizophrenia, 5-HT$_4$ receptors may be an attractive target for improving cognition in schizophrenia, since currently available atypical APDs generally lack significant affinity for 5-HT$_4$ receptors [**215**].

3.2.6 5-HT$_6$ Receptors

Several atypical antipsychotics, including clozapine and olanzapine, and some tricyclic antidepressants, such as amitriptyline, and clomipramine,

were found to have high affinity for 5-HT_6 receptors [**218**] prompting significant efforts to understand its possible role in schizophrenia and other neuropsychiatric disorders. When antisense oligonucleotides were used to decrease the level of 5-HT_6 receptor expression in rats, the rats exhibited an increased number of yawns and stretches that could be blocked by atropine, suggesting a role of the 5-HT_6 receptor in the control of cholinergic neurotransmission [**219**]. In addition, the selective 5-HT_6 receptor antagonist SB-271046 has been shown to improve memory retention in the water maze test of spatial learning and memory [**220,221**]. Likewise, 5-HT_6 antagonists can enhance the release of cortical DA and glutamate, and may also have long-term neurotrophic actions in normal rats [**222**]. Thus, it appears likely that 5-HT_6 receptors may have an important future role in the treatment of cognitive deficits in neuropsychiatric illnesses such as Alzheimer's disease and schizophrenia. The 5-HT_6 antagonist GSK (SB)-742457 is currently in phase II clinical trials [**223**].

3.2.7 5-HT_7 Receptors

The 5-HT_7 receptor exerts important roles in circadian rhythms, mood and sleep. 5-HT_7 receptors are found in relatively high concentrations in hippocampus, thalamus and hypothalamus, with generally lower levels in cortex and amygdale [**224**]. 5-HT_7 receptors bind certain atypical APDs (for example, amisulpride, clozapine, risperidone) with high affinity and may have important roles in learning and memory as well as antidepressant

actions [**225**]. Moreover, the specific 5-HT_7 receptor antagonist SB-258741 produced a positive result in one animal model for schizophrenia [**226**].

3.3 Adrenergic Targets

3.3.1 Alpha$_1$-adrenergic Receptors

Although many typical and atypical APDs (see **Table 1 and Figure 1**) possess alpha$_1$-adrenoreceptor blocking properties, the putative significance of this effect for their clinical efficacy in schizophrenia has remained unclear [**227**]. Alpha$_1$-adrenoceptor shows a remarkable high density in the PFC, expressed in pyramidal and GABAergic neurons [**102-104**, Santana et al., IntJNP submitted for publication]. Available data suggest that alpha$_1$-adrenoreceptor blockade may modulate the PFC function making the PFC a particularly sensitive area to the action of atypical antipsychotic drugs [**228,229**]. However, the therapeutic potential of alpha$_1$-adrenoreceptor blockade in schizophrenia has been neglected due to its cardiovascular effects, despite the fact that selective antagonist prazosin enhanced the antipsychotic actions of DA D_2 receptor blockade [**230**].

3.3.2 Alpha$_2$-adrenergic Receptors

The central noradrenergic system projects from the *locus coeruleus* to the prefrontal cortex where alpha$_2$-adrenergic receptors appear to play an important role in cognitive functioning, as previously described [**111,112**]. Indeed, the alpha$_2$-adrenergic receptor agonists, clonidine and guanfacine,

have been shown to improve cognition in various preclinical and clinical studies [**110,231,232**]. In addition, patients randomized to risperidone plus guanfacine showed significant improvement on tasks of working memory and attention compared with patients receiving typical antipsychotics plus guanfancine [**231**]. However, clozapine and other atypical APDs have potent antagonist properties at alpha$_2$-adrenergic receptors [**233**], an effect that may contribute to the “atypicality” of the atypical APDs by enhancing mesocortical dopaminergic neurotransmission over the mesolimbic pathway. Several preclinical and clinical studies provide evidence that the alpha$_2$-adrenergic receptor antagonist idazoxan enhances the antipsychotic efficacy of typical and atypical APDs [**234-236**]. This effect has been suggested to account for the superior effect of clozapine to increase PFC DA release [**236**]. However, clozapine's action on PFC DA release appears dependent exclusively on the activation of PFC 5-HT$_{1A}$ receptors [**127,170**]. Overall, alpha$_2$-adrenergic receptor blockade may be important in developing new drugs for schizophrenia that can improve cognition, balancing alpha$_2$-adrenergic receptor activity to achieve both antipsychotic and procognitive efficacy may be challenging.

3.3.3 Add-on Strategies: Augmentation of PFC Dopaminergic Activity

Many studies implicate prefrontal catecholamine function in cognition [**52,110,237,238**]. In addition, previous experimental observations show also striking similarities between the factors governing DA and NE release in the medial PFC. Preclinical studies showed that NE terminals in PFC

largely contribute to the control of mesocortical DA output (but not in mesolimbic pathway) by co-releasing DA and taking up DA via NE transporter (NET) [**239-244**]. Moreover, a marker and selective enhancement of DA function in medial PFC is feasible through the combined administration of NET blockers such as reboxetine and alpha$_2$-adrenergic receptor antagonists (e.g. RX-821002, mirtazepine] [**244,245**]. Recently, we showed that this latter effect occurs when these drugs are administered alone or in combination with typical (haloperidol) and atypical (clozapine) APDs, which suggests its potential usefulness to improve cognitive deficits as well as to treat negative symptoms in patients with schizophrenia [**244**] (**Fig. 4**). Likewise, an improvement of antipsychotic-like effects and increases of cortical DA neurotransmission were also found after adjunctive treatment of a NET inhibitor with $D_{2/3}$ antagonist raclopride or atypical olanzapine APD [**241,246**].

Clinically, initial attempts to use alone reboxetine as add-on therapy to haloperidol in the treatment of schizophrenia failed to show significant progress [**247**]. However, this was effective in patients with prominent depressive and negative symptoms who showed substantial improvement on all clinical ratings [**248**]. In addition, adjunctive treatment with the NET inhibitor atomoxetine to schizophrenic patients treated with atypical APDs was found to activate certain brain areas related to working memory [**249**]. Consequently, this opens the way to perform more comprehensive clinical trials in which reboxetine or other NET blockers, used as antidepressants, can be combined with alpha$_2$-adrenergic antagonists in order to test their

clinical efficacy on cognitive dysfunction in schizophrenia and other psychiatric disorders (**Fig. 5**).

4. CONCLUDING REMARKS: CHALLENGES IN DRUG DISCOVERY

The first family of antipsychotic drugs appeared during the 1950s and some members are still used 50 years later due to their robust effectiveness for the acute and chronic treatment of schizophrenia and related psychotic disease. These agents are successful in improving the psychotic symptoms of schizophrenia in 60–70% of patients. However, the limitation of classical APDs is the incidence of severe side effects (extrapyramidal effects, hiperporlactinemia, tardive dyskinesia, etc.) in up to 40 % of the patients. The so-called “atypical” drugs show an equal or slightly better efficacy than older drugs and have a different profile of side effects, in which weight gain and metabolic problems rank first. Nevertheless, they have an overall better tolerance than conventional drugs and they have reached a great commercial success, despite the above side effects. Likewise, the cognitive dysfunction is estimated to occur in 75-85% of patients with schizophrenia, and although, there is some evidence for the superiority of atypical over classical APDs in improving cognitive performance, the benefits are relatively small [**35**]. Hence, to some extent, the situation is similar to that in the antidepressant field: selective serotonin reuptake inhibitors (SSRIs), and selective serotonin and norepinephrine inhibitors (SNRI), which make up ~90% of the market worldwide, are better tolerated drugs than first-

generation tricyclic antidepressants due to the absence of severe side effects, but they are not more effective than the older drugs.

Given the clinical and neurobiological complexity of schizophrenia, and the heterogeneity of the patient population, it would seem logical to develop compounds with at least a degree of D_2 receptor affinity that also bind one or more favored targets such as 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, alpha$_2$-adrenergic receptors, among others. Another option is to develop single-target drugs/strategies can be used as adjuncts to APDs to augment efficacy by targeting specific symptom dimensions of schizophrenia. Additionally, other potential targets in antipsychotic drug development may arise from research on metabotropic glutamate receptors (mGluR), because a mGluR2/3 receptor agonist has showed antipsychotic activity [**250**]; a topic not covered by the present review.

Cognitive dysfunction is a major feature of schizophrenia, where much effort has been focused on developing cognitive-enhancing drugs. In addition of monoaminergic targets described above, a variety of molecular targets with pro-cognitive effects in schizophrenia have been identified. For example, significant progress has been made in recent years on elucidating various susceptibility genes in schizophrenia, including dysbindin, neuroregulin 1, COMT, others [**251**]. Interestingly, many of these genes appear to be related to the control of synaptic plasticity and glutamatergic transmission. Another strategy involves the role of neurotrophic factors, where BDNF may play a role in neuronal and glial proliferation, and the maintenance of synaptic plasticity [**252,253**]. Thus, strategies to enhance

neurotrophic factor action may be able to prevent progression of schizophrenia. Moreover, altering neurotransmitter signaling by targeting intracellular cascades has long been suggested to be a future approach to novel therapeutic agents such as phosphodiesterase (PDE) inhibitors, particularly at PDE10A [**254**]. However, there is no proven mechanism for developing such drugs as yet and many barriers still exist in the translation from basic science to drug discovery.

Although hypotheses of cognitive deficits in schizophrenia separately implicate dopaminergic, cholinergic, noradrenergic, serotonergic, glutamatergic and/or GABAergic deficits, it is very likely that the actual circuit dysfunction involves interactive changes between most of these systems. Accordingly, such complexity may limit the potential effectiveness of agents targeting a single mechanism, and more integrative approaches may be necessary. Taken together, the discovery of effective novel therapeutic agents for the treatment of schizophrenia will require continued research efforts and collaboration by both academic and industrial laboratories. At regarding, various initiatives in America and Europe such as MATRICS, CNTRICS and NEWMED programs have the renewed hope to understand the molecular and functional pathophysiological mechanisms operative in schizophrenia.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

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Figures 1-5

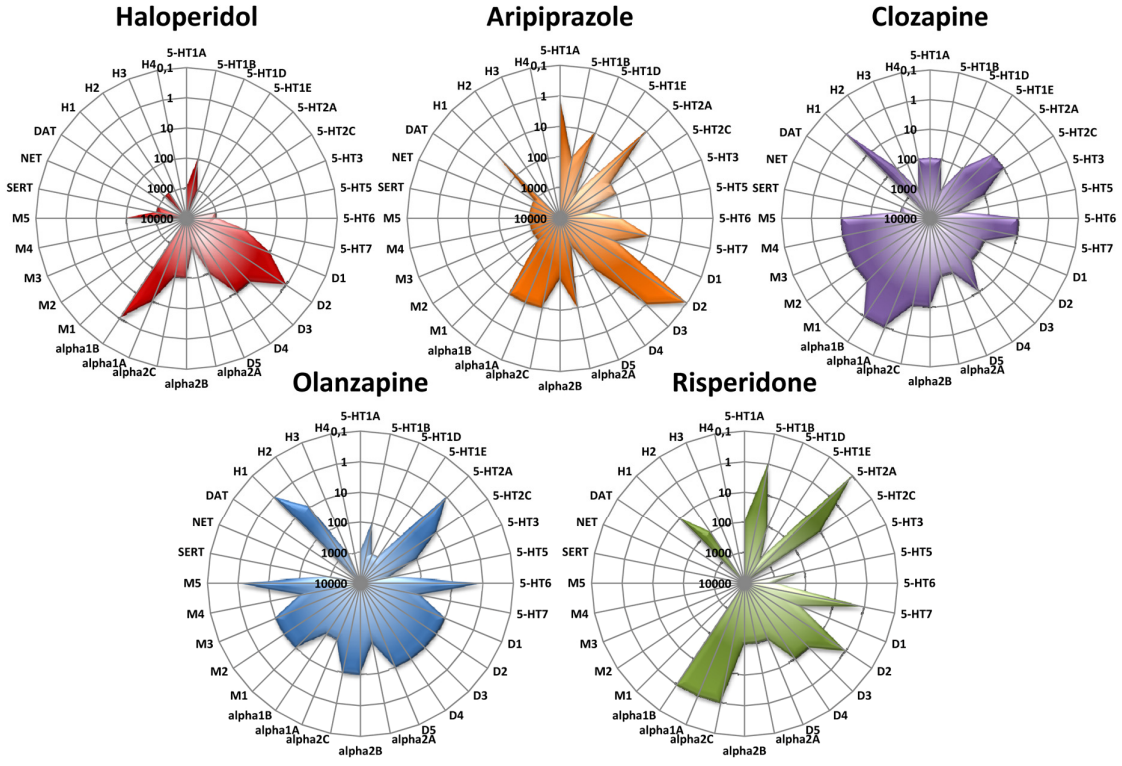

Fig. (1). "Radar" representations of the receptor binding profile for some APDs. Affinities are indicated in Ki values. Thus, the greater distance from the central node of the radar plot indicates the higher drug affinity for a specific binding site. Data were taken from PSDP Ki dababase (http://kidb.cwru.edu/) and Roth et al., [**26**].

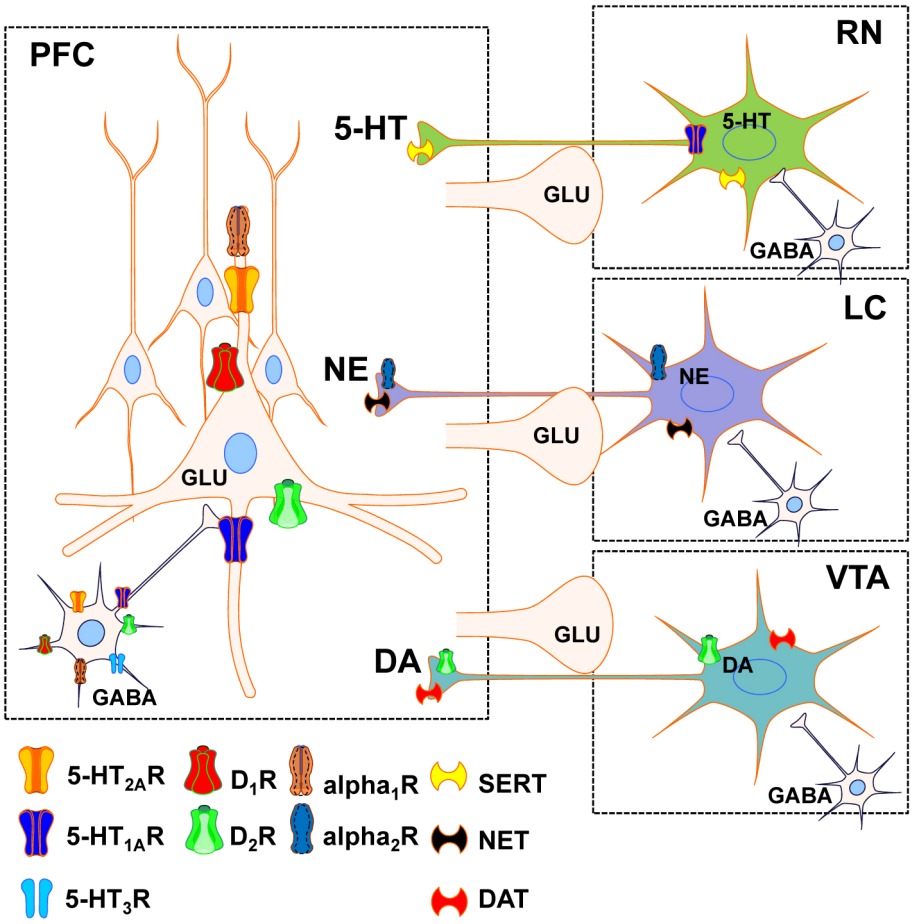

Fig. (2). Schematic representation of the anatomical and functional relationships between the medial prefrontal cortex (PFC) and the brainstem monoaminergic nuclei. The PFC receives a dense innervation from the brainstem monoaminergic nuclei such as the raphe nuclei (RN, serotonin – 5-HT), *locus coeruleus* (LC, norepinephrine - NE) and ventral tegmental area (VTA, dopamine - DA), which are reciprocally connected with the PFC [48-51,55]. In turn, 5-HT, NE and DA neurons modulate the activity of pyramidal cells in mPFC through various receptors such as 5-HT_{1A}, 5-HT_{2A}, alpha$_1$-adreno receptors, D_1, D_2, among others which are expressed by pyramidal and GABAergic neurons, respectively [101,123-126]. These receptors are identified as potential molecular targets for treating cognitive dysfunction in schizophrenia.

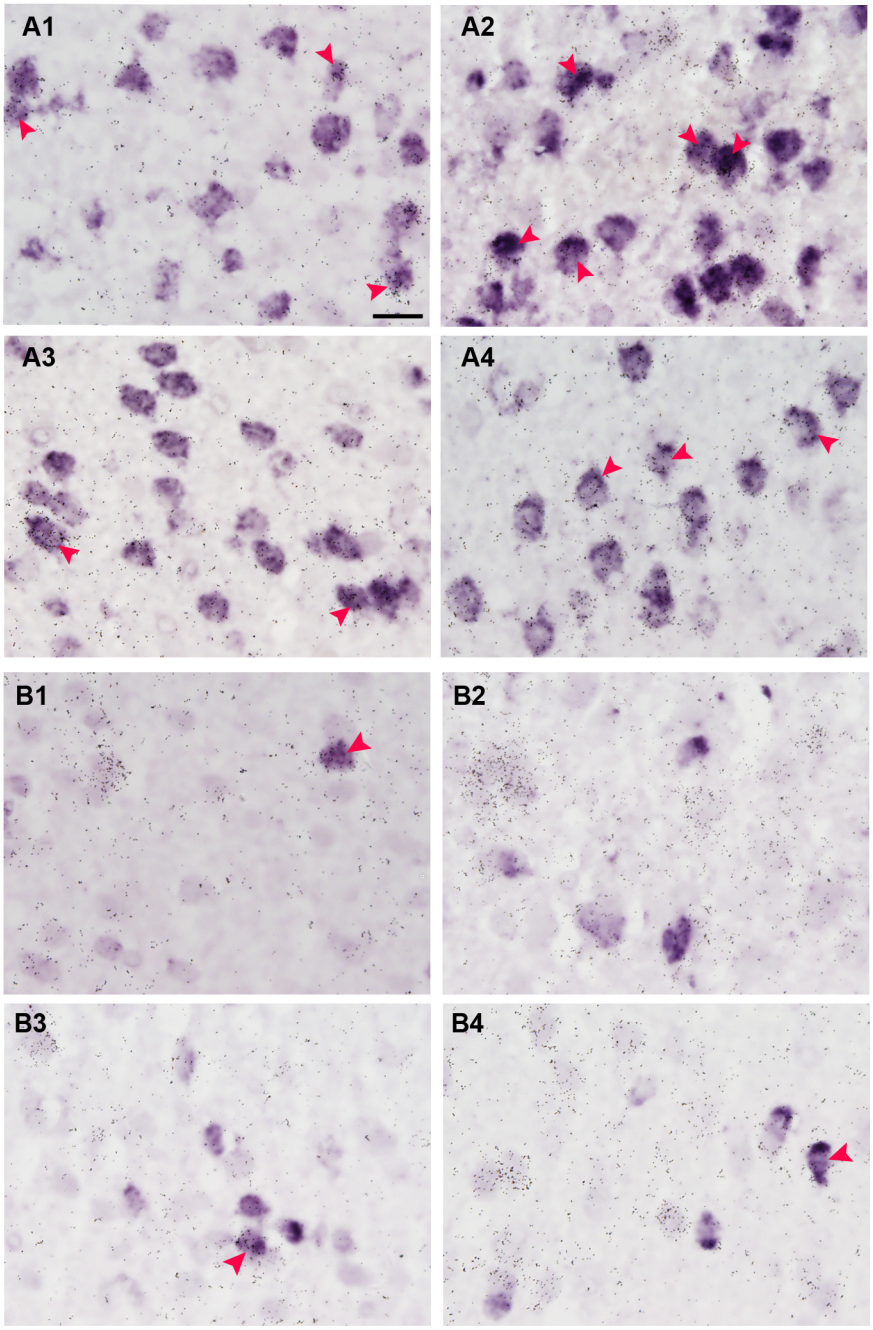

Fig. (3). Expression of dopamine (DA) and serotonin (5-HT) receptors in prelimbic area of medial prefrontal cortex (mPFC), layers V-VI of rats assessed by double *in situ* hybridization. **(A)** High magnification photomicrographs showing pyramidal cells (vGLUT1-positive, digoxigenin-labeled oligonucleotides) seen as dark cellular profiles expressing DA D_1 and D_2 receptor mRNAs (**A1** and **A2** figures, respectively) and 5-HT_{1A} and 5-HT_{2A}

receptor mRNAs (**A3** and **A4** figures, respectively). **(B)** High magnification photomicrographs showing GABAergic cells (GAD-positive, digoxigenin-labeled oligonucleotides) seen as dark cellular profiles expressing DA D_1 and D_2 receptor mRNAs (**B1** and **B2** figures, respectively) and 5-HT_{1A} and 5-HT_{2A} receptor mRNAs (**B3** and **B4** figures, respectively). Probes for each receptor mRNA are labeled with ^{33}P, and are seen as silver grain precipitates. Red arrowheads mark some double-labeled cells. Bar = 20μm. Adapted from Santana et al., [**101**,**123**]

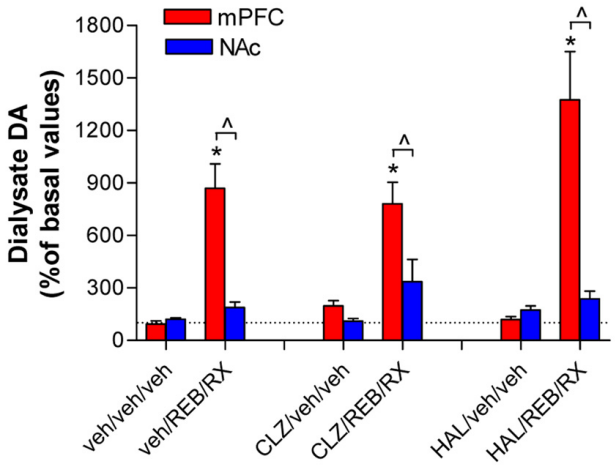

Fig. (4). Bars show the average effect of the combination treatment of NET inhibitor reboxetine (REB, 3 mg/kg, i.p.) plus selective alpha$_2$-adrenoreceptor antagonist RX-821002 (RX, 1 mg/kg, s.c.) on dopamine (DA) release in medial prefrontal cortex (mPFC) and nucleus accumbes (NAc) of adult rats assessed by *in vivo* microdialysis. Rats were pretreated with (i) vehicle, (ii) atypical APD clozapine (CLZ, 3 mg/kg, s.c.) or (iii) classical APD haloperidol (HAL, 0.1 mg/kg, s.c.). Note that a marker and selective enhancement of DA output in mPFC is feasible through the combined treatment of NET blockers and alpha$_2$-adrenoreceptor antagonists. Data are mean ± SEM of AUC of fractions 12-16, expressed as percentage of baseline. *$p < 0.001$ *vs*. control treatment (veh/veh/veh) and ^$p < 0.01$ for mPFC versus NAc. Adapted from Masana et al., [244]

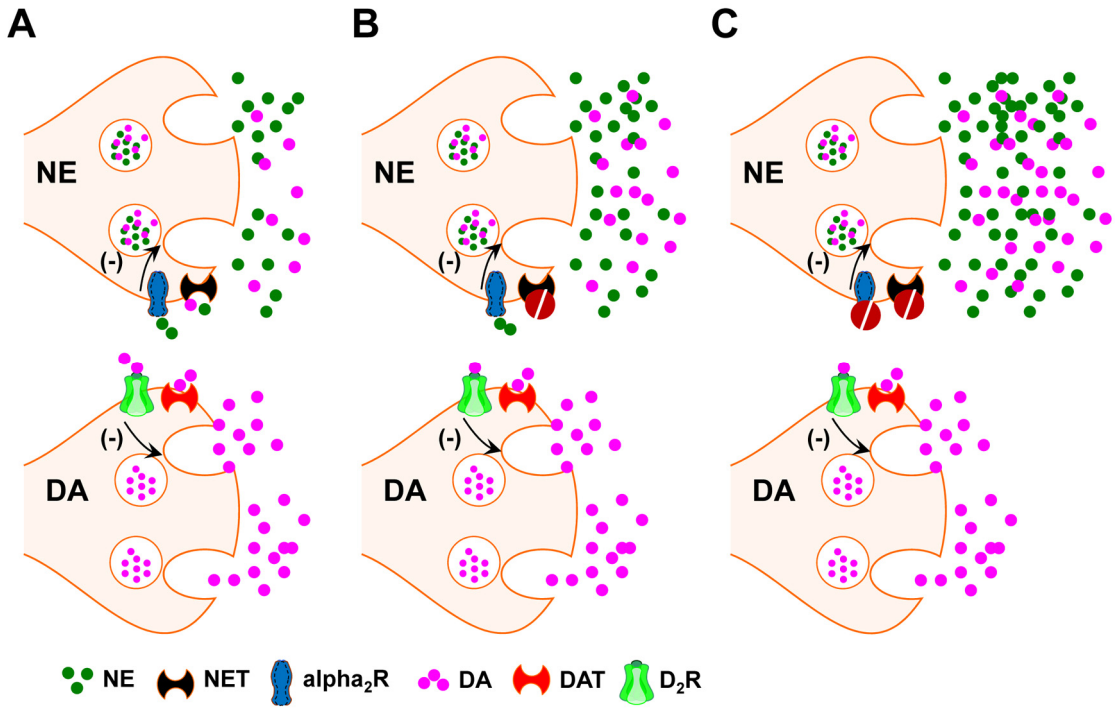

Fig. (5). Schematic representation of the contribution of norepinephrine transporter (NET) inhibition (reboxetine) and alpha$_2$-adrenoreceptor antagonism (RX-821002, mirtazepine) in NE terminals on the control of extracellular DA concentration in PFC. **(A)** In a physiological situation, DA can be co-released with NE by noradrenergic terminals and/or taken up by NET, given the similar affinity of the membrane transporters for both monoamines. **(B)** The moderate increase in extracellular DA levels in PFC evoked by reboxetine probably results from two opposing factors: an elevation resulting from NET blockade itself, and a reduction resulting from the activation of alpha$_2$-adrenoceptors in NE axons. Activation of somatodendritic alpha$_2$-adrenoceptors in the LC (not shown in the figure) also contributes to attenuate catecholamine release through a reduction of the firing rate of noradrenergic neurons after systemic reboxetine administration. **(C)** The co-treatment with RX821002 or mirtazepine removes the alpha$_2$-adrenoceptor-mediated negative feedback, and markedly potentiates the increase in extracellular DA and NE levels evoked by alpha$_2$-adrenoreceptor antagonists. Adapted from Masana et al., [244,245]

Table 1. Relative receptor pharmacology of marketed antipsychotic drugs

	Typical (first generation)	Atypicals (second and third generation)						
Receptor	**Haloperidol**	**Clozapine**	**Olanzapine**	**Quetiapine**	**Risperidone**	**Amisulpride**	**Aripiprazole**	**Ziprasidone**
D_1	++	++	++	+	+	-	+	+
D_2	++++	+	++	+	+++	+++	++++	+++
D_3	+++	+	++	+	+++	+++	++++	+++
D_4	+++	++	++	++	+++	-	++	++
5-HT_{1A}	-	+	-	+	+	-	+++	+++
5-HT_{2A}	-	++	+++	++	++++	-	+++	++++
Alpha$_1$	+++	+++	++	+++	++++	-	++	++
Alpha$_2$	-	+	+	-	++	-	-	-
H_1	++	+++	+++	++	++	-	-	++
M_1	-	+++	+++	+	-	-	-	-

Adapted from Abi-Dargham and Laruelle [9], using an *in vitro* and *in vivo* screening techniques.

Table 2. Expression of some monoaminergic receptor mRNAs in prelimbic cortex of rat

	Prelimbic Cortex		
Receptor	**Layer II-III**	**Layer V**	**Layer VI**
D_1 positive			
Pyramidal neurons	19.0 ± 3.0	21.0 ± 2.0	38.0 ± 3.0
GABAergic neurons	28.0 ± 1.0	30.0 ± 2.0	38.0 ± 4.0
D_2 positive			
Pyramidal neurons	5.0 ± 1.0	25.0 ± 2.0	13.0 ± 1.0
GABAergic neurons	5.0 ± 1.0	8.0 ± 2.0	17.0 ± 2.0
5-HT_{1A} positive			
Pyramidal neurons	n.e.	61.0 ± 2.0	n.e.
GABAergic neurons	n.e.	20.0 ± 1.0	n.e.
5-HT_{2A} positive			
Pyramidal neurons	n.e.	52.0 ± 3.0	n.e.
GABAergic neurons	n.e.	34.0 ± 1.0	n.e.
5-HT_3 positive			
Pyramidal neurons	n.e.	n.e.	n.e.
GABAergic neurons	4.1 ± 0.5	1.5 ± 0.3	2.0 ± 0.1
Alpha$_1$ positive			
Pyramidal neurons	80.0 ± 3.0	79.0 ± 8.0	59.0 ± 2.0
GABAergic neurons	79.0 ± 5.0	72.0 ± 5.0	57.0 ± 8.0

Data are means ± SEM of the mean of 3 rats (4 adjacent sections per rat) and show the percentage of neurons of each type (pyramidal or GABAergic) expressing several monoaminergic receptors in superficial, intermediate, or deep layers of the prelimbic area in the medial PFC of rat. n.e. not examined. Adapted from Amargós-Bosch et al., [124], Santana et al., [101,123] and Puig et al., [126]