CNS Spectrums (2020), **25**, 343–351. © Cambridge University Press 2019
doi:10.1017/S109285291900083X

REVIEW ARTICLE

The role of dopamine D_3 receptors in the mechanism of action of cariprazine

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Cariprazine is a new atypical antipsychotic drug (APD) with a unique pharmacodynamic profile, different from both typical and atypical APDs. Specifically, cariprazine acts as a partial agonist at the dopamine (DA) D_2 and D_3 receptors and serotonin 5-HT_{1A} receptors, and as an antagonist at the 5-HT_{2B} receptors. Moreover, it shows moderate affinities for adrenergic, histaminergic, and cholinergic receptors that are involved in mediating the side effects characteristic of typical APDs. In this review, we discuss the contribution of DA D_3 receptors (D_3Rs) in the etiology and pathophysiology of schizophrenia and the potential benefits that may be associated with a more selective targeting of D_3R by APDs, as compared to other dopaminergic and non-dopaminergic receptor subtypes. Cariprazine, by acting on D_3Rs, ameliorates anhedonia and cognitive deficits in animal models based on environmental or pharmacological manipulation. The reviewed results support the potential benefits of cariprazine in treating negative symptoms and cognitive deficits of schizophrenia, and therefore representing a promising approach in addressing the unmet clinical needs for the improved treatment of this serious neuropsychiatric disorder.

Received 12 October 2018; Accepted 23 February 2019; First published online 23 April 2019

Key words: Dopamine D_3 receptors, cariprazine, antipsychotic drugs, schizophrenia, negative symptoms, cognitive deficits.

Introduction

Dopamine (DA) is a key brain neurotransmitter that contributes to the control of different behaviors, including locomotion, cognition, reward, and motivation.[1–4] Its activity is mediated by two receptor families: the "D_1-like" family includes D_1 and D_5 receptors that stimulate adenylyl cyclase activity, while the "D_2-like" receptors (D_2, D_3, and D_4) inhibit the production of cAMP and also regulate other systems, including K+ channels, AKT (AKT serine/threonine kinase)–GSK3 (glycogen synthase kinase 3 beta)–βarrestin as well as intracellular calcium levels.[5–7]

Alterations of dopaminergic functions have been associated with the pathophysiology of different brain disorders, including Parkinson's disease, attention-deficit hyperactivity disorder (ADHD), bipolar and mood disorders, schizophrenia, and drug addiction. The association between DA and schizophrenia is particularly complex since a dopaminergic hyperactivity in the mesolimbic regions appears to contribute to psychotic symptoms, such as hallucinations and delusions, as opposed to a dopaminergic hypoactivity in cortical regions, which underlies the negative symptoms and cognitive deficits of the disease. The management of these "opposite" dopaminergic dysfunctions may represent a major challenge for pharmacological intervention. With this respect, currently available antipsychotic drugs (APDs) are quite effective in managing the positive symptoms of schizophrenia, but they are less effective in addressing the negative symptoms and cognitive deficits[8] even if a partial agonist like aripiprazole has been shown to improve quality of life in schizophrenic patients compared to paliperidone.[9] On these bases, a better control of these core symptoms, which often persist during periods of clinical stability and can be severe enough to impair the daily functional activities of patients,[10,11] represents a critical aspect for the improvement of the clinical outcome.

Considering that DA-related dysfunction represents a hallmark in schizophrenia, there is always a great deal of interest in developing novel strategies to modulate the "dopaminergic" function with the aim to address clinical "unmet needs." Among different potential targets, there has been an increasing interest in DA D_3 receptors (D_3Rs), whose modulation may improve the outcome

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of schizophrenia treatment. In this review, we discuss the contribution of these receptors in the etiology and pathophysiology of schizophrenia and the potential benefits that may be associated with a more selective targeting of DA D_3Rs by APDs, as compared to other dopaminergic and non-dopaminergic receptor subtypes.

From D_2 to D_3 Receptor

DA D_3Rs, which were identified in 1990,[12] show higher affinity for endogenous DA, as compared to D_2, and their distribution is restricted to limbic regions, including the islands of Calleja, the shell of nucleus accumbens (NAc), and the olfactory tubercles, with much lower levels of expression in basal ganglia or other brain structures. Although restricted, the distribution of D_3Rs appears to be critically involved in the regulation of important functions, such as motivation, emotion, and reward as well as cognition,[12-14] which represent key pathologic domains for several psychiatric disorders, including schizophrenia.[15]

DA D_3Rs are scarcely found in the majority of DA symmetric synapses, while they are detected at the levels of asymmetric synapses at the head of dendritic spines, a localization that is in sharp contrast with DA D_1Rs and DA D_2Rs, which are either pre-synaptic or spread all over dendrites and dendritic spines in neurons of the caudate putamen and NAc.[14,16] Since asymmetrical synapses are typically glutamatergic (Glu) and may be located at some distance from DA terminals, it is expected that DA D_3Rs may play a peculiar role in the modulation of neurotransmitter circuitry. Indeed, on the basis of the higher affinity of endogenous DA for D_3Rs, over other DA receptors, it has been hypothesized that DA D_3Rs would be less sensitive to rapid (phasic release) than slower (tonic release) changes in DA concentration. Moreover, considering that phasic release in mesolimbic areas mediates the responses to salient stimuli (such as reward-relevant event or potential threat), while tonic release mediates the amplitude of the response,[17] it is feasible that enhanced DA D_3Rs sensitivity would result in the aberrant assignment of salience to elements one's experiences as it may occur in schizophrenia.[18] Moreover, D_3Rs may exert a tonic inhibition of DA neurons in the ventral tegmental area (VTA) projecting to the NAc by stimulating GABA release, whereas D_3Rs expressed on dopaminergic neurons of the VTA inhibit DA synthesis and release. Taken together, these observations support a negative control of D_3-mediated signaling on DA neurons, either by acting directly on its autoreceptors (located both at nerve terminals and in the cell bodies) or by modulating GABA release, which eventually leads to a downregulation of DA release in PFC.[15,16]

Similar to the majority of GPCR, D_3Rs may form homo- and heterodimers[19] with D_2Rs[20] and D_1Rs,[21,22] as well as with the adenosine A_2 receptors,[23] and they may also interact with nicotinic acetylcholine receptors (nAChRs),[24] a property that could increase their functional heterogeneity. Moreover, it has been recently shown that D_3Rs positively regulate several intracellular pathways such as Erk1/2 and Akt through G protein-dependent as well as independent mechanisms,[25,26] suggesting that their functional activity may be different depending on the interactions with other membrane receptors or transduction proteins, a concept known as bias agonism.

The high density of the D_3Rs in the ventral striatum, as compared to the dorsal part, increased the expectation that selective D_3 antagonists would exert antipsychotic activity with minimal or no side effects including extrapyramidal side effects (EPS)[27] and catalepsy.[14,28] Moreover, antagonists at D_3Rs can increase cognitive performance and may reverse cognitive deficits in rodents and monkeys.[29-33] Additionally, D_3Rs are implicated in executive functions that are often disrupted in schizophrenia.[34] Interestingly, overexpression of D_3Rs specifically in the ventral striatum is sufficient to decrease motivation, an important component of the negative symptoms in schizophrenia, and this may be due to secondary effects on DA D_1Rs.[35] While it can be inferred that D_3R antagonism represents a relevant strategy to ameliorate the negative symptoms, a major unmet need in the treatment of schizophrenia,[15,36,37] it must be pointed out that DA D_3R stimulation may also be neurotrophic and neuroprotective on DA neurons during development.[26,38]

On these bases, partial agonism at D_2Rs and D_3Rs may represent a promising approach, according to the concept of "dopamine stabilization," since a single compound may increase or decrease dopaminergic activity according to the state of a given circuit.[39,40] Specifically, in patients with schizophrenia, this strategy reduces the hyperactivity of the dopaminergic tone in the mesolimbic regions while increasing dopaminergic hypoactivity in the frontal cortex. The first partial D_2/D_3 agonist approved for the treatment of schizophrenia was aripiprazole, and there are now two drugs that share a similar mechanism of action: brexpiprazole and cariprazine.[41] We will specifically focus on cariprazine, based on its prominent affinity for DA D_3Rs over other DA receptor subtypes.

Cariprazine

Cariprazine is a piperazine derivative developed by Gedeon-Richter in Hungary. In 2015, the drug was approved in the USA for the treatment of schizophrenia and for the treatment of acute manic or mixed episodes associated with bipolar I disorder. Cariprazine has a unique pharmacodynamic profile rendering it different from other typical and atypical APDs.[42] Indeed, it is a partial agonist at DA D_2Rs and D_3Rs as well as 5-HT_{1A}

https://doi.org/10.1017/S109285291900083X Published online by Cambridge University Press

receptors while acting as antagonist at 5-HT_{2A} and 5-HT_{2B} receptors. Moreover, it shows low to moderate affinity for other neurotransmitter receptors that may be responsible for the occurrence of important side effects.[43]

Cariprazine shares unique pharmacological signatures with two other DA partial agonists: aripiprazole and brexpiprazole in terms of their partial agonist activity at DA D_2Rs, D_3Rs, and 5-HT_{1A}Rs, as well as antagonistic activity at 5-HT_{2A}Rs. However, cariprazine has the strongest affinity for DA D_3Rs, as partial agonist, followed by aripiprazole and brexpiprazole, whereas brexpiprazole has the strongest affinity for DA D_2Rs, as a partial agonist, followed by aripiprazole and cariprazine.[41,44–46] Cariprazine's selective actions as a potent DA D_3R partial agonist [intrinsic activity of 0.70][43] may stabilize abnormalities in DA neurotransmission in different brain regions including the cerebral cortex and therefore may improve negative symptoms and cognitive deficits in schizophrenia patients. The activity of cariprazine on 5-HT_{1A}Rs and 5-HT_{2A}Rs may further improve psychotic or manic symptoms while maintaining a benign EPS profile.[41,44,45]

Cariprazine is safe and effective at the dose range of 1.5–6 mg daily. It is mainly metabolized by CYP3A4 (and, to a lesser extent, CYP2D6), generating two active metabolites (desmethyl cariprazine and di-desmethyl cariprazine). The steady state is reached around weeks 1–2 for cariprazine and desmethyl cariprazine and around weeks 4–8 for di-desmethyl cariprazine.[47] The presence of these two active metabolites may prolong the efficacy of the parent compound, although more information is needed with respect to the efficacy of such metabolites. The pharmacokinetic of cariprazine and its metabolites are not affected in a clinically relevant degree by CYP2D6 poor metabolizer status, age, weight, sex, or race.[48] Cariprazine and its metabolites are weak inhibitors of CYP1A2, CYP2C9, CYP2D6, CYP3A4, CYP2C19, and CYP2E1. Moreover, pharmacokinetic interactions of cariprazine with substrates of these enzymes are not likely to occur, while the dose of cariprazine has to be reduced if co-administered with a strong CYP3A4 inhibitor such as ketoconazole. The association with CYP3A4 inducers, such as carbamazepine, is not recommended.

Since 2008, several studies and reviews have been published on the efficacy, safety, and tolerability of cariprazine in humans.[48,49] As an example, cariprazine was effective in adult patients diagnosed with schizophrenia and generally well tolerated in three 6-week randomized double-blind, placebo-, and/or active-controlled phase-II and phase-III studies. The treatment was not associated with alterations in metabolic parameters, prolactin production, prolongation of QT interval, or substantial increases in body weight.[50] Nevertheless, the incidence of akathisia and EPS was higher with cariprazine than with placebo. Accordingly, open-label extension studies (NCT00839852–NCT01104792) reported that both low and high doses of cariprazine were generally well tolerated and did not result in any new safety concerns.[51–55] Moreover, cariprazine treatment was generally associated with a low rate of sedation and weight gain.[56–58]

Notably, one of the main unmet needs in schizophrenia is the limited ability of APDs to improve negative symptoms. It is important to underline that negative symptoms may be distinguished between primary (an integral part of the disease) and secondary that develop as a consequence of the positive symptoms or as side effects of some APDs.[59] Therefore, it is important to perform clinical trials that enroll only patients with primary negative symptoms. In this context, a recent randomized, placebo-controlled clinical trial that compared the effects of cariprazine vs. risperidone on negative symptoms in schizophrenia patients found a significant superiority of one APD versus another given in monotherapy.[10] Cariprazine showed a significant effect on primary negative symptoms after 14 weeks of treatment and continued to improve until the endpoint, at week 26. The reduction of the Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS) was paralleled by a greater improvement in functioning (self-care, interpersonal relationship, and social activities), with a consequent increase in the quality of life[60] as previously shown for aripiprazole but not with paliperidone[9] emphasizing the added value of the partial agonism activity.

Molecular Effects of Cariprazine

A series of studies examined the long-term effects of cariprazine administration on regulation of different DA (D_1, D_2, and D_3), 5-HT (5-HT_{1A} and 5-HT_{2A}), and glutamate (NMDA and AMPA) receptor subtypes in rat forebrain regions that represent limbic, cortical, and extrapyramidal brain systems, and then compared the effects to other typical and atypical antipsychotics on the same receptors from previous studies to determine if cariprazine would induce atypical-like effects on forebrain neurotransmitter receptors.

DA receptors

Long-term administration of cariprazine resulted in significant increases in DA D_3R levels in olfactory tubercle, Islands of Calleja, and shell of NAc.[61] Cariprazine-induced increases in forebrain DA D_3Rs appear to be unique to this drug since the repeated administration of other typical and atypical APDs including haloperidol, fluphenazine, clozapine, olanzapine, risperidone, and asenapine failed to alter levels of DA D_3Rs.[62–65] It appears that cariprazine with its potent DA D_3R affinity and occupancy[43,66] is able to replace endogenous DA and occupy DA D_3Rs to the level required to trigger receptor

https://doi.org/10.1017/S109285291900083X Published online by Cambridge University Press

TABLE 1. Summary of the D_3 receptor preclinical studies

Model	Protocol	Effect	Reference
Apomorphine-induced climbing	Injection of apomorphine 10 min before the test. Cariprazine (0.1–1 mg/kg) administered 1, 4, 8, 16, and 24 h before apomorphine.	Inhibition of climbing behavior induced by apomorphine.	66
Conditioned avoidance response	Cariprazine (0.1–1 mg/kg) administered 1 h before the test.	Inhibition of conditioned avoidance response in rats.	66
Novelty- and stimulant-induced motor activity	Cariprazine (0.05–0.5 mg/kg) administered 1 h before the test. Hypermotility induced by PCP or MK-801 injection.	Inhibition of hyperlocomotion induced by novelty, PCP and MK-801.	66
Catalepsy	Cariprazine injected 30 min before the test.	No induction of catalepsy.	66
Water-labyrinth learning performance	Cariprazine (0.01–0.3 mg/kg) injected 1 h before the first swim. Scopolamine injected as amnestic agent.	Protection against scopolamine-induced deficit.	66
Lower lip retraction	Lower lip scored 30, 60, 90, and 120 min after cariprazine treatment (0.5, 1, and 2 mg/kg).	Induction of lower lip retraction.	66
DOI-induced head twitch	Cariprazine (0.05–0.5 mg/kg) injected 1 h before the DOI-treatment.	Inhibition of DOI-induced head-twitch.	66
Elevated plus maze	Cariprazine (0.005, 0.01, 0.02, 0.08, and 0.15 mg/kg) administered before the test.	The higher doses affect locomotor activity.	79
Social recognition/interaction and social recognition memory	Cariprazine (0.005, 0.01, and 0.02 mg/kg) and PCP (1 mg/kg) administered 1 h and 30 mi prior the test, respectively. WT and D3KO mice were tested.	PCP injection impaired social interaction and social recognition memory in both genotypes. Cariprazine exerted its effect only in WT mice.	79
SWM	Cariprazine (0.005, 0.01, and 0.02 mg/kg) and PCP (1 mg/kg) administered 1 h and 30 min prior the test, respectively. WT and D3KO mice were tested.	Cariprazine pre-treatment blocked the effects of PCP only in WT mice.	79
Attention-set-shifting task (ASST)	Cariprazine (0.005, 0.01, and 0.02 mg/kg) and PCP (1 mg/kg) administered 1 h and 30 min prior the test, respectively. WT and D3KO mice were tested.	Cariprazine pre-treatment blocked PCP-induced impairment only in WT mice.	79
Sucrose consumption test	Rats were exposed for 7 weeks to the chronic mild stress (CMS) paradigm. Cariprazine (0.01, 0.03, 0.065, 0.25, and 1.0 mg/kg) was administered for 5 weeks starting from the third week of stress.	Cariprazine restored the CMS-induced decrease of sucrose consumption.	85
Locomotor activity and rearing behaviour in a novel arena.	Cariprazine (0.1–0.3 mg/kg) injected 30 min prior the test to rats prenatally treated with PCP and housed in social isolation from weaning for 5 weeks.	Cariprazine attenuated the hyperactivity produced by combined neonatal PCP and social isolation rearing.	83
NOR task	Cariprazine (0.1–0.3 mg/kg) injected 30 min prior the test to rats prenatally treated with PCP and housed in social isolation from weaning for 5 weeks.	Cariprazine reversed the impairment in NOR produced by combined neonatal PCP and social isolation rearing.	83
Social interaction	Cariprazine (0.1–0.3 mg/kg) injected 30 min prior the test to rats prenatally treated with PCP and housed in social isolation from weaning for 5 weeks.	Cariprazine partially normalized the social interaction deficit.	83
NOR test	Cariprazine (0.05,0.1, and 0.25 mg/kg) injected 1 h prior the test 7 days after the treatment with PCP for 7 days (PCP injection start at PND7).	Cariprazine at the lower doses normalized the defect due to PCP.	81
Reversal learning paradigm	Cariprazine (0.05, 0.1, and 0.25 mg/kg) injected 1 h prior the test 7 days after the treatment with PCP for 7 days (PCP injection start at PND7).	Cariprazine improved in a dose-dependent manner the impairment due to PCP treatment.	81
Social interaction paradigm	Cariprazine (0.05, 0.1, and 0.25 mg/kg) injected 1 h prior the test 7 days after the treatment with PCP for 7 days (PCP injection start at PND7).	Cariprazine at the lower doses reversed PCP-induced deficits.	81
Sucrose consumption test	Mice were exposed for 25 days to the chronic mild stress (CMS) paradigm with a concomitant treatment with cariprazine (0.03, 0.1, and 0.2 mg/kg). WT and D3KO mice were tested.	Cariprazine at the higher dose normalized the reduced sucrose consumption induced by CMS exposure in WT but not in D3KO mice.	84

(*Continued*)

https://doi.org/10.1017/S109285291900083X Published online by Cambridge University Press

TABLE 1. (*Continued*)

Model	Protocol	Effect	Reference
Novelty-induced hypophagia test	Mice were exposed for 25 days to the chronic mild stress (CMS) paradigm with a concomitant treatment with cariprazine (0.03, 0.1, and 0.2 mg/kg). WT and D3KO mice were tested.	Cariprazine at the higher doses corrected the phenotype caused by CMS exposure in WT but not in D3KO mice.	84
5-choice serial reaction time task (5-CRSTT)	Rats were treated for 2 days with PCP. For the following 3 days animals were administered with cariprazine (0.03, 0.1, and 0.3 mg/kg) and PCP 1 h and 30 min prior the test, respectively.	Cariprazine treatment reduced PCP-induced increases in appropriate responding.	80

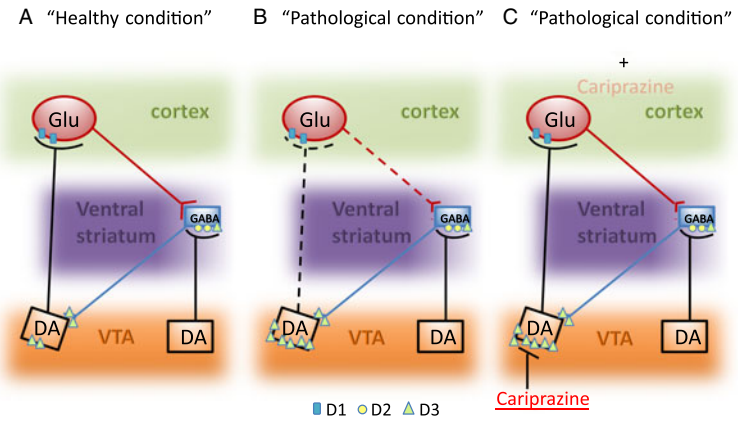

FIGURE 1. Schematic representation of DA D_3R dysfunction in schizophrenia and the potential impact of cariprazine treatment. In pathological condition (panel B), as compared to the healthy condition (panel A), the overexpression of the D_3Rs located in the DA neuron projecting from the VTA to the cortex leads to an inhibition of DA release in the prefrontal cortex, which may eventually reduce the Glu output. Cariprazine (panel C), by acting as partial agonist on the DA D_3Rs of the mesocortical pathways, may reduce the "pathologic" inhibition thus leading to a normalization of DA release within the prefrontal cortex.

upregulation.[67] DA receptor upregulation is typically observed with repeated administration of DA receptor antagonists. However, despite its DA D_3R partial agonist activity, cariprazine increased DA D_3Rs, which may suggest it is acting as an antagonist at D_3Rs in vivo. Cariprazine may normalize disturbances in DA D_3R-mediated neurotransmission in patients with schizophrenia and bipolar mania, and improve their mood, cognitive, and executive functions.[68,69]

Repeated administration of cariprazine also increased DA D_2Rs in frontal cortex and hippocampus, an effect shared by other atypical APDs.[64,65] Such changes may contribute to the beneficial therapeutic effects of cariprazine in schizophrenia and bipolar mania. Higher doses of cariprazine increased DA D_2Rs in basal ganglia, which may account for the higher incidence of akathisia (9% vs. 5%) and extrapyramidal disorder (12% vs. 5%), compared with placebo-treated patients, in clinical trials.[70,71]

Serotonin and glutamate receptors

The long-term effects of cariprazine were not limited to DA receptors. Repeated administration of cariprazine increased 5-HT_{1A}Rs in the cerebral cortex, an effect consistent with the effects of other atypical APDs such as olanzapine, risperidone, quetiapine, and asenapine on the same receptor in the same brain.[65,72,73] The effects of these APDs may result from direct blockade of 5-HT_{1A} receptors or from secondary effects as a result of combined actions of these drugs on D_2 and 5-HT_{2A} receptors. These effects further validate cortical 5-HT_{1A}R as common targets that mediate the beneficial actions of cariprazine and other atypical antipsychotics. Interestingly, long-term administration of cariprazine did not alter 5-HT_{2A}R levels in the cerebral cortex. In contrast, several other atypical APDs significantly decreased these receptors in the same brain region, suggesting that 5-HT_{2A}Rs are less likely to contribute to the mechanism of action of cariprazine in vivo.[65,72,73] It is possible that long-term cariprazine treatment with the

https://doi.org/10.1017/S109285291900083X Published online by Cambridge University Press

selected doses did not achieve the in vivo occupancy of 5-HT_{2A} receptors needed to trigger changes in the concentrations of these receptors in different brain regions.

Long-term administration of cariprazine decreased NMDA receptors in caudate putamen and NAc, an effect shared by atypical and not typical APDs.[72,74-76] Downregulation of striatal NMDA receptors by cariprazine and several atypical APDs may contribute, at least in part, to the benign extrapyramidal profile of atypical antipsychotic agents.[77] Cariprazine also decreased NMDA and increased AMPA receptors in the hippocampus, which may improve psychotic symptoms by normalizing abnormalities in hippocampal Glu neurotransmission postulated to occur in schizophrenia patients.[72,78]

Behavioral Effects of Cariprazine

Acute administration of cariprazine was effective in behavioral tests with face validity for the positive symptoms of schizophrenia, including the blockade of amphetamine-induced hyperactivity, inhibition of apomorphine-induced climbing, as well as antagonism of the locomotor stimulating effect of non-competitive NMDA antagonists.[66]

Cariprazine's effects on cognitive functions were investigated using animal models based on the administration of the muscarinic antagonist scopolamine or the non-competitive NMDA receptors antagonist phencyclidine (PCP). Acute injection of cariprazine was able to normalize scopolamine-induced deficits in a water labyrinth task with a bell-shaped dose-response pattern, while risperidone, olanzapine, and aripiprazole were less effective.[66] Moreover, acute cariprazine pretreatment (0.08–0.15 mg/kg) significantly attenuated deficits on social recognition memory (hippocampal/perirhinal function), spatial working memory (SWM), and extradimensional attention set-shifting (prefrontal cortex-dependent), disrupted by acute PCP treatment.[79] Importantly, the positive effects of cariprazine were not observed when the drug was given to PCP-treated DA D_3R KO mice, suggesting that, despite the complex mechanisms through which PCP elicits cognitive deficits, DA D_3R modulation is critical in mediating the effects of cariprazine.[79]

A recent study has shown that 5 days of PCP injection increased incorrect, premature, and timeout responses in the 5-choice serial reaction task.[80] Interestingly, and different from aripiprazole, a 3-day treatment with cariprazine at a dose of 0.03 mg/kg attenuated PCP-induced deficits without producing non-specific response suppression.[80] Neill and colleagues have also produced evidence on the ability of cariprazine to normalize the behavioral abnormalities observed after a sub-chronic treatment with PCP in female rats. PCP-induced alterations in cognition and social behavior, which were still present one week at the end of PCP administration, were normalized by a single dose of cariprazine (0.05 mg/kg) administered 1 h before the behavioral tests. Interestingly, risperidone (0.16 mg/kg) was only able to attenuate the PCP-induced avoidance, suggesting a larger effect of cariprazine.[81] The efficacy of cariprazine was also investigated in an experimental model that combines PCP treatment and social isolation. This model is of particular interest since the manipulations are conducted early in life and caused long-term neurodevelopmental, behavioral, structural, and neurochemical alterations with a translational relevance for a spectrum of symptoms seen in schizophrenia.[82] Interestingly, a single dose of cariprazine (0.1–0.3 mg/kg) or aripiprazole (3 mg/kg) reduced the hyperactivity and reversed the cognitive deficits in the novel object recognition (NOR) test that were observed in rats exposed to a combination of PCP and social isolation.[83] Moreover, only cariprazine was able to correct pro-social behavioral and body-sniffing, which may reflect a potential effectiveness of cariprazine, but not aripiprazole, in treating negative symptoms.[83]

Recent studies have also shown that cariprazine is able to exert antidepressant- and anxiolytic-like behaviors in stress-based models, which mimic an important etiological mechanism for clinical depression and anxiety.[84,85] In particular, prolonged treatment with cariprazine was able to normalize the anhedonic-like behavior, measured as reduction of sucrose intake, induced by chronic stress exposure, an effect that appears to rely on the ability to modulate D_3Rs.[84,85] Indeed, even if DA D_3R knock-out (KO) mice do not exhibit anxiety and depressive-like behavior,[86,87] and the effect of prolonged stress exposure is similar between wild-type and DA D_3R KO mice, cariprazine treatment was not able to normalize anhedonia in transgenic mice exposed to chronic stress.[84] Cariprazine, similar to aripiprazole, was also able to attenuate the anxiolytic-like behavior in chronically stressed rats, as indicated by its ability to reduce drinking latency in the novelty-induced hypophagia test.[84] Furthermore, it has been recently demonstrated that cariprazine, possibly through the modulation of D_3Rs, increases DA, serotonin, and norepinephrine efflux in rat NAc and hippocampus, an effect that may also contribute to the procognitive, prosocial, and antipsychotic-like actions of cariprazine in animal models.[88]

Conclusions

In summary, cariprazine represents a novel APD with a peculiar receptor signature that is primarily characterized by a partial agonism at DA D_3Rs and D_2Rs, with higher affinity for the former receptor subtype when compared to partial agonists such as aripiprazole and brexpiprazole. Interestingly, preclinical studies, as summarized in Table 1, have clearly demonstrated the efficacy of cariprazine not only in regulating positive symptoms but

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also on negative symptoms and cognitive deterioration of schizophrenia. While the precise mechanism of action of cariprazine remains to be determined, its high affinity for the DA D_3Rs is likely to play a key role, as supported by studies conducted in DA D_3 KO mice.

Similar to other APDs, cariprazine improves positive symptoms primarily through its activity on D_2R. Conversely, the partial agonism at the D_3R may represent the main mechanism through which the drug ameliorates negative symptoms and cognitive deficits. Indeed, several evidences support the concept that D_3Rs can participate in the complex and heterogeneous alterations of the dopaminergic system in schizophrenia. In particular, an overexpression of the D_3Rs on the dopaminergic neuron projecting from the VTA to the PFC, therefore acting as autoreceptor, may reduce the dopaminergic activity leading to a hypofunction at cortical level. Such defects can be ameliorated by cariprazine that, by modulating these receptors, will ultimately improve the treatment of negative symptoms as well as cognitive deficits, which represent important elements for the functional disability found in schizophrenia patients (Figure 1).

Disclosures

Marco A. Riva received compensation as speaker/consultant from Lundbeck, Otzuka, Sumitomo Dainippon Pharma, and Sunovion, and received research grants from Lundbeck, Sumitomo Dainippon Pharma, and Sunovion. Frank I. Tarazi received research grants from Lundbeck and Sunovion. Giorgio Racagni received consulting fees and/or honoraria from Indena, Servier, and Recordati. Francesca Calabrese has nothing to declare.

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