Involvement of 5-HT$_{1A}$ and 5-HT$_{2A}$ Receptors but Not $\alpha_2$-Adrenoceptors in the Acute Electrophysiological Effects of Cariprazine in the Rat Brain In Vivo

Anna Herman, Mostafa El Mansari, Nika Adham, Béla Kiss, Bence Farkas, and Pierre Blier

Mood Disorders Research Unit, University of Ottawa Institute of Mental Health Research, Ottawa, Ontario, Canada (A.H., M.E.M., P.B.); Allergan, Madison, New Jersey, United States (N.A.); and Gedeon Richter Plc, Budapest, Hungary (B.K., B.F.)

Received June 6, 2018; accepted October 4, 2018

ABSTRACT

Cariprazine, an orally active and potent dopamine D$_3$-preferring D$_3$/D$_2$ receptor partial agonist, is approved to treat adults with schizophrenia (in the United States and Europe) and manic or mixed episodes associated with bipolar I disorder (in the United States). Cariprazine also displays partial agonism at serotonin [5-hydroxytryptamine (5-HT)] 5-HT$_{1A}$ receptors and antagonism at 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors in vitro. The study objective was to determine whether cariprazine leads to functional alterations of monoamine systems in vivo via electrophysiological recordings from anesthetized rats. Dorsal raphe nucleus (DRN), locus coeruleus (LC), and hippocampus pyramidal neurons were recorded, and cariprazine was administered systemically or locally through iontophoresis. In the DRN, cariprazine completely inhibited the firing activity of 5-HT$_{1A}$ neurons, which was fully reversed by the 5-HT$_{1A}$ receptor antagonist, WAY100635. In the LC, cariprazine reversed the inhibitory effect of the preferential 5-HT$_{2A}$ receptor agonist, 2,5-dimethoxy-4-iodoamphetamine, on norepinephrine (NE) neurons (ED$_{50}$ = 66 µg/kg) but did not block the inhibitory effect of the $\alpha_2$-adrenergic receptor agonist, clonidine. Cariprazine, iontophoresized into the hippocampus, diminished pyramidal neuronal firing through activation of 5-HT$_{1A}$ receptors, while its concomitant administration did not dampen the suppressant effect of 5-HT. These results indicate that, in vivo, cariprazine acted as a 5-HT$_{1A}$ autoreceptor agonist in the DRN, a 5-HT$_{2A}$ receptor antagonist in modulating the firing activity of LC NE neurons, and a full agonist at 5-HT$_{1A}$ receptors mediating the electrophysiological effect of 5-HT on pyramidal neurons. The modulatory actions of cariprazine on these monoaminergic systems may contribute to its therapeutic effectiveness in patients with depressive episodes.

Introduction

Cariprazine (in the United States: Vraylar; in Europe: Reagila) is a novel dopamine (DA) D$_3$-preferring D$_3$/D$_2$ receptor and serotonin [5-hydroxytryptamine (5-HT)] 5-HT$_{1A}$ receptor partial agonist that has been approved to treat schizophrenia (in the United States and Europe) and manic or mixed episodes associated with bipolar I disorder (in the United States). It was recently reported that adjunctive cariprazine was efficacious in patients who had an inadequate response to their medications used to treat major depressive disorder (Durgam et al., 2016a). Cariprazine has also shown efficacy in improving symptoms of depressive episodes in patients with bipolar I disorder (Durgam et al., 2016b). Unlike aripiprazole, another DA receptor partial agonist indicated for the treatment of schizophrenia and bipolar disorder, cariprazine acts as a D$_3$/D$_2$ receptor partial agonist with higher binding affinity and selectivity (5- to 8-fold) for D$_3$ versus D$_2$ receptors and as a more potent antagonist at 5-HT$_{2A}$ receptors in vitro (Lawler et al., 1999; Kiss et al., 2010; Maeda et al., 2014). In addition to these properties, cariprazine was shown in vitro to be a partial agonist at 5-HT$_{1A}$ receptors in hippocampal tissue, a high-affinity antagonist at 5-HT$_{2B}$ receptors, and to have moderate affinity for histamine type 1 receptors (Kiss et al., 2010).

The role of 5-HT$_{1A}$ receptors in depression has been demonstrated by findings that the 5-HT$_{1A}$ receptor agonists buspiroline and gepirone are effective antidepressants, either as a monotherapy or in combination with selective serotonin reuptake inhibitors (SSRIs) for acute treatment and relapse prevention (Trivedi et al., 2006; Bielski et al., 2008; Fabre et al., 2011). In addition, activation of 5-HT$_{1A}$ receptors by selective agonists such as 8-OH-DPAT increases DA release in the prefrontal cortex (Arborelius et al., 1993; Li et al., 2004; Assié et al., 2005).

Several lines of evidence suggest that blockade of 5-HT$_{2A}$ receptors in combination with SSRIs treatment may contribute to substantial therapeutic benefits in major depressive disorder (Blier and Szabó, 2005). Indeed, medications that block 5-HT$_{2A}$ receptors, such as aripiprazole, quetiapine, risperidone, and olanzapine, as well as mirtazapine and mianserin, are effective augmentation strategies in combination with SSRIs (Nelson and Papakostas, 2009; Kennedy et al., 2016). The only property that the aforementioned drugs have in common is their capacity to block 5-HT$_{2A}$ receptors. Thus, it is

**ABBREVIATIONS:** 5-HT, 5-hydroxytryptamine (serotonin); CA3, cornu ammonis 3; DA, dopamine; DOI, 2,5-dimethoxy-4-iodoamphetamine; DRN, dorsal raphe nucleus; LC, locus coeruleus; NE, norepinephrine; SSRI, selective serotonin reuptake inhibitor.
likely that the 5-HT$_{2A}$ receptor antagonistic property of these agents acts by removing the inhibitory effects of SSRIs on norepinephrine (NE) systems (Szabo and Blier, 2002; Seager et al., 2004; Dremencov et al., 2007; Chernoloz et al., 2009, 2012).

In vitro studies are necessary to identify potential therapeuetic compounds, but it is also important to study the activity of a drug in vivo to have a thorough mechanistic understanding. Prior experiments of this nature have been conducted to characterize the effects of cariprazine on DA neurons (Delcourte et al., 2018) but not on 5-HT or NE systems. To this end, the objectives of the present study were to determine the in vivo effects of acute cariprazine administration at 5-HT$_{1A}$ autoreceptors in the dorsal raphe nucleus (DRN), postsynaptic 5-HT$_{1A}$ receptors in the hippocampus, 5-HT$_{2A}$ receptors controlling NE neuron firing in the locus coeruleus (LC), and $\alpha_{2}$-adrenergic autoreceptors within the LC using electrophysiological techniques.

Materials and Methods

**Animals.** The experiments were carried out on male Sprague-Dawley rats (Charles River Laboratories, St. Constant, QC, Canada) weighing 250–350 g and housed in groups of two per cage, under standard laboratory conditions (12-hour light-dark cycle with food and water ad libitum). In vivo extracellular recordings were carried out in chloral hydrate–anesthetized rats (400 mg/kg, intraperitoneal [i.p.]) that were mounted in a stereotaxic apparatus. Supplemental doses of the anesthetic (100 mg/kg, i.p.) were given to maintain constant anesthesia and prevent nociceptive reaction to pinching of the hind paws. Body temperature was maintained at 37°C throughout the experiment via a thermistor-controlled heating pad. Prior to electrophysiological recordings, a catheter was inserted in a lateral tail vein for systemic intravenous injection of pharmacologic agents. Recordings were generally carried out within 30–60 minutes after achieving complete anesthesia. All experiments were carried out in accordance with the Canadian Council on Animal Care and the local Animal Care Committee (Royal Ottawa Institute of Mental Health Research, Ottawa, Canada).

**Compounds.** The preferential 5-HT$_{2A}$ receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI), the $\alpha_{2}$-adrenergic agonist clonidine, and the selective 5-HT$_{1A}$ receptor antagonist WAY100635 were dissolved in 5% lactic acid and distilled water for systemic intravenous injection of pharmacologic agents. Recordings were generally carried out within 30–60 minutes after achieving complete anesthesia. All experiments were carried out in accordance with the Canadian Council on Animal Care and the local Animal Care Committee (Royal Ottawa Institute of Mental Health Research, Ottawa, Canada).

**Recording of DRN 5-HT Neurons.** Putative 5-HT neurons were recorded by positioning single-barrel glass micropipettes at the following coordinates (in millimeters from lambda): anterior/posterior, 1.1 to −1.2; mediolateral, 1.0–1.3; and dorsal/ventral, 5.0–7.0. The following criteria were used to identify NE neurons: regular firing rate (1.0–5.0 Hz), long duration (0.8–1.2 milliseconds) of the action potential, and brisk excitatory response followed by a short period of inhibition in reaction to a nociceptive pinch of the contralateral hind paw (Aghajanian et al., 1977). To test the effect of cariprazine on 5-HT$_{2A}$ receptors, NE neurons were suppressed by the preferential 5-HT$_{2A}$ receptor agonist DOI (Szabo and Blier, 2001). Following an inhibition period, cumulative intravenous doses of cariprazine were administered to antagonize the inhibitory effect of DOI. The reversing effect of cariprazine was quantified relative to the stable baseline firing activity for over at least a 60-second interval preceding the intravenous injection.

**Systemic Intravenous Injections.** Systemic intravenous injections of various drugs were used to obtain their net effect on the firing rate of NE neurons, since it is one of the main determinants of NE transmission. DOI had to be injected intravenously and not locally applied, because the 5-HT$_{2A}$ receptors controlling the NE neuron firing activity are not located in the LC (Szabo and Blier, 2001).

**Recording of Pyramidal Neurons in the CA3 Region of the Hippocampus.** The CA3 pyramidal neurons were recorded by positioning multibarrel glass micropipettes at the following coordinates (in millimeters from lambda): anterior/posterior, 3.5–4.2; mediolateral, 4.0–4.2; and dorsal/ventral, 3.5–4.5. Because most CA3 pyramidal neurons are not spontaneously active in chloral hydrate-anesthetized rats, a small ejection current (+2 to −2 nA) was applied to the quisqualate barrel to activate them to be within their physiologic firing range (10–15 Hz) (Runck, 1975). Partial or full agonism of cariprazine on 5-HT$_{1A}$ receptors cannot be assessed in vivo using systemic injections. Therefore, it was assessed by comparing the inhibitory effect of 5-HT, per se, to the inhibitory effect of concomitant ejection of 5-HT and cariprazine, following restoration of the firing rate to the same level as before by increasing quisqualate ejection. In this paradigm, coapplication of a partial agonist reduces the inhibitory effect of 5-HT, whereas coapplication of a full agonist does not change the inhibitory effect of 5-HT, provided the ensuing concentration of the agent tested against 5-HT (cariprazine here) is initially sufficient to induce inhibition of the firing activity of pyramidal neurons by at least 50% (Blier and de Montigny, 1990; Dong et al., 1998; Ghanabari et al., 2009, 2010; Oosterhof et al., 2014). To ascertain whether the inhibitory effect of 5-HT and cariprazine was mediated by 5-HT$_{1A}$ receptors, the inhibitory effect of iontophoretic 5-HT and cariprazine application was compared before and after administration of the selective 5-HT$_{1A}$ receptor antagonist WAY100635.

**Data Analysis.** Electrophysiological recordings were made using Spike2 software version 6.17 (Cambridge Electronic Design, Cambridge, UK). Quantification of firing rates was performed using Spike2. When
appropriate, groups were analyzed with a paired t test or with repeated-measures analysis of variance followed by a Holm-Sidak method. All data were analyzed with GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, CA). Data are presented as mean ± S.E.M.; P < 0.05 was considered significant.

Results

Effect of Cariprazine on the Firing Activity of DRN 5-HT Neurons. The role of cariprazine in inhibiting the firing activity of 5-HT neurons via 5-HT1A autoreceptors was investigated in the DRN. Cumulative intravenous injections of 50 μg/kg of cariprazine decreased the firing activity of 5-HT neurons (n = 15 rats; one neuron per animal). This effect was subsequently reversed by the selective 5-HT1A receptor antagonist WAY100635, indicating that cariprazine was acting as an agonist at the 5-HT1A autoreceptors in vivo (Fig. 1A).

Although the response was dose dependent for each neuron tested, the degree of firing inhibition for a given dose varied considerably. Indeed, the dose required to completely inhibit the firing rate ranged from a minimum of 150 μg/kg to a maximum of 850 μg/kg (Fig. 1B). However, 80% of the tested neurons (n = 12 of 15) were completely inhibited by cumulative intravenous doses of cariprazine within a range of 150–350 μg/kg. Upon detailed analysis, there was no correlation between the initial baseline firing rate of an individual 5-HT neuron and the cariprazine dose required to completely inhibit the firing (Fig. 1C).

Effect of Cariprazine on Postsynaptic 5-HT1A Receptors on Pyramidal Neurons in the Hippocampus. Microiontophoretic application of cariprazine significantly inhibited the firing activity of pyramidal neurons, as did 5-HT (Fig. 2A). There was no statistically significant difference between the degree of inhibition induced by 5-HT alone compared to when it was concomitantly applied with cariprazine (P > 0.05; Fig. 2, A and B), indicating that cariprazine acted as a full agonist at 5-HT1A receptors in vivo in the hippocampus.

The effects of ejecting cariprazine and 5-HT in the CA3 pyramidal neurons were assessed after an intravenous injection of the selective 5-HT1A receptor antagonist WAY100635 (50 μg/kg) to confirm that these two substances were acting through the 5-HT1A receptor. Indeed, the degree of inhibition induced by both cariprazine and 5-HT was significantly reduced by the antagonist (**P < 0.01, ***P < 0.001, respectively; Fig. 2, C and D).

Fig. 1. (A) Integrated firing rate histogram of a single 5-HT neuron showing its response to four cumulative intravenous injections of cariprazine and the subsequent reversal with an intravenous dose of the selective 5-HT1A antagonist WAY100635. (B) Relationship between the number of 5-HT neurons showing 100% inhibition of firing and the dose of cariprazine necessary to achieve the complete suppression of firing. One neuron was recorded per rat. (C) No significant correlation between the degree of firing activity of 5-HT neurons and the dose of cariprazine necessary to achieve complete inhibition.
Effect of Cariprazine on the Firing Activity of LC NE Neurons: Role of 5-HT2A Receptors and α2-Adrenergic Receptors. The preferential 5-HT2A receptor agonist DOI (100 μg/kg, i.v.) induced near complete cessation of NE neuronal firing (Fig. 3A). Cumulative intravenous injections of 50 μg/kg of cariprazine restored the firing activity up to 70% of the baseline level, with an ED50 value of 65.5 μg/kg (Fig. 3; n = 7).

As shown in Fig. 4, in the presence of cariprazine, the effect of the α2-adrenoceptor agonist clonidine was compared with its effect under control conditions. After cariprazine pretreatment, clonidine fully inhibited the firing activity of NE neurons upon dosing with two cumulative injections (10 μg/kg, i.v.) as it did in control conditions (Fig. 4). The effects of clonidine on NE neuronal firing were reversed by administration of the α2-adrenoceptor antagonist idazoxan (1 mg/kg, i.v.), indicating that cariprazine did not block α2-adrenoceptors (Fig. 4).

Discussion

In the DRN, cariprazine fully inhibited the firing activity of 5-HT neurons. This effect was reversed by the selective 5-HT1A receptor antagonist WAY100635, which indicated that cariprazine acted as an agonist in vivo at the 5-HT1A autoreceptors in this brain structure. Although cumulative doses inducing inhibition varied for each 5-HT neuron tested, the effect of cariprazine was dose dependent for each neuron; nevertheless, the majority of neurons were inhibited by doses ranging between 150 and 350 μg/kg. A potential role of α1-adrenoceptors in altering the responsiveness of 5-HT neurons to cariprazine, as is the case with olanzapine and clozapine (Sprouse et al., 1999), can be excluded since cariprazine has very weak or negligible affinity for these receptors (Kiss et al., 2010). It could be assumed that the varied neuronal responsiveness of 5-HT1A autoreceptors to cariprazine stems from differences in baseline firing of individual neurons, since a previous study suggested that 5-HT neurons with slow firing activity are more sensitive to 5-HT receptor agonists than neurons with faster discharge (Jacobs et al., 1983). In the present study, however, this variable response was not related to the baseline firing rate of individual neurons. Such variation in the degree of inhibition was unexpected because all selective 5-HT1A receptor agonists and other agents with 5-HT1A receptor partial agonist activity (e.g., aripiprazole and brexpiprazole) tested in this paradigm yielded a tight dose-response relationship upon systemic administration, unlike cariprazine (Blier and de Montigny, 1990; Dong et al., 1998; Rueter and Blier, 1999; Dahan et al., 2009; Oosterhof et al., 2014). Interestingly, both aripiprazole and brexpiprazole display greater in vitro affinity for 5-HT1A receptors than
Cariprazine but were less potent than cariprazine in activating the 5-HT_{1A} autoreceptors (Dahan et al., 2009; Oosterhof et al., 2014; Citrome, 2015). Therefore, a potential explanation for the wide range of cariprazine doses needed to inhibit 5-HT neurons may be due to the balance of the inhibitory effect of 5-HT_{1A} receptor activation versus the excitatory action of D_{2}-like receptors for different 5-HT neurons (Chernoloz et al., 2009). Indeed, 5-HT neurons are endowed with D_{2}-like receptors that mediate an excitatory influence on neuronal firing (Aman et al., 2007; Katz et al., 2010). This explanation can be envisioned if it is assumed that the 5- to 8-fold greater binding affinity and selectivity of cariprazine for D_{3} versus D_{2} receptors, compared with aripiprazole and brexpiprazole (which show a lower affinity for D_{3} receptors and a higher selectivity for D_{2} vs. D_{3} receptors than cariprazine), exert a larger excitatory effect on some 5-HT neurons. Interestingly, D_{3} receptor expression has been demonstrated by binding assays in the median and dorsal raphe nuclei of the midbrain (Stanwood et al., 2000), and thus may also influence 5-HT neuronal firing in this region. However, further studies using selective tools are needed to explore the specific role of the D_{3} receptor on 5-HT neuronal activity. At this point, it is unclear whether the variability in the response of 5-HT neurons to cariprazine translates into a functional difference compared, for example, to other DA receptor partial agonists such as brexpiprazole and aripiprazole. Nevertheless, although cariprazine and aripiprazole had a superior effect on mood symptoms when compared with placebo, the magnitude of their effect appears to be similar in patients with schizophrenia (Durgam et al., 2015).

In the hippocampus, cariprazine did not reduce the effectiveness of the endogenous ligand 5-HT at postsynaptic 5-HT_{1A} receptors when the two compounds were applied concomitantly. This indicates that cariprazine acted as a full 5-HT_{1A} receptor agonist in this brain region. Similar to cariprazine, brexpiprazole has also been shown to act as a full agonist at the postsynaptic 5-HT_{1A} receptors in the hippocampus (Oosterhof et al., 2014). It is also important to note that agents acting on 5-HT_{1A} receptors can have heterogeneous effects at 5-HT_{1A} receptors in different brain areas. For instance, studies of the 5-HT_{1A} receptor agonist/5-HT_{2A} receptor antagonist flibanserin revealed that it acts as a full agonist at presynaptic 5-HT_{1A} receptors in the DRN and at postsynaptic 5-HT_{1A} receptors in the medial prefrontal cortex, but as a partial agonist at the postsynaptic 5-HT_{1A} receptors in the CA3 region of the hippocampus (Reuter and Blier, 1999). Moreover, it was reported that selective activation of these postsynaptic receptors enhances 5-HT transmission and DA release in the medial prefrontal cortex (Chung et al., 2004). Indeed, activation of 5-HT_{1A} receptors (by 5-HT_{1A} receptor agonists) was shown to increase DA release in the medial prefrontal cortex (Ichikawa et al., 2001; Díaz-Mataix et al., 2005).

A previous study has shown that both aripiprazole and cariprazine decreased 5-HT turnover rate in mouse prefrontal cortex through an action on 5-HT_{1A} receptors (Kiss et al., 2010).
In various in vitro assays, cariprazine was shown to act either as a partial agonist (Kiss et al., 2010) or full agonist depending on the assay system used. The present in vivo study found that cariprazine acted rather as a full agonist at 5-HT1A receptors controlling the firing activity of pyramidal neurons in the hippocampus. It has been suggested that a partial agonist can behave differently depending on the level of receptor reserve; for example, the partial agonist may behave as expected or even as an antagonist in tissue with low or negligible levels of receptor reserve, but in the presence of high levels of receptor reserve that same partial agonist may behave like a full agonist instead (Kenakin, 1987). This is, however, not the case with the in vivo electrophysiological response reported herein because, with the approach used in this study, both partial and full 5-HT1A receptor agonists have been identified in the DRN and hippocampus (Blier and de Montigny 1990; Dong et al., 1998; Ghanbari et al., 2009, 2010; Oosterhof et al., 2014). It is nevertheless possible that these responses are partially dependent on the coupling between specific 5-HT1A receptors and the signal transduction mediating their response (Valdizán et al., 2010). Indeed, in the hippocampus 5-HT1A receptors are coupled to adenylyl cyclase but also to potassium channels, the latter being involved in the electrophysiological responses measured in this study, and both of which have displayed differential properties in previous studies (Yocca et al., 1992; Blier et al., 1993).

Cariprazine acted as a potent antagonist at 5-HT2A receptors on LC NE neurons, since it reversed the inhibitory effect of the preferential 5-HT2A receptor agonist DOI. These receptors are located on GABA neurons that control the activity of NE neurons (Haddjeri et al., 1997; Szabo and Blier, 2002). Interestingly, administration of YM992 (a 5-HT2A receptor antagonist and an inhibitor of 5-HT reuptake) or blockade of 5-HT2A receptors by the selective 5-HT2A receptor antagonist MDL100907 during treatment with the SSRI citalopram was shown to synergistically increase cortical NE levels, which were measured by microdialysis (Hatanaka et al., 2000). Furthermore, blockade of 5-HT2A receptors by various medications, such as risperidone, aripiprazole, and olanzapine, reverses the inhibitory effect of SSRIs on LC NE neurons (Seager et al., 2004; Dremencov et al., 2007; Chernoloz et al., 2009). Despite the lower in vitro binding affinity of cariprazine for 5-HT2A receptors when compared with other drugs commonly used to

![Fig. 4. Representative integrated firing rate histograms illustrating inhibition of NE neuron firing activity by clonidine (A), and the lack of effect of cariprazine on this activity following pretreatment with cariprazine (B and C). Note that this inhibition is reversed by the intravenous injection of the α2-adrenoceptor idazoxan.](image-url)
treat psychosis and mania (Ghanbari et al., 2009; Oosterhof et al., 2014), its in vivo 5-HT2A receptor antagonist potency for reversing the inhibitory effect of DOI was similar to those medications. The α2-adrenergic autoreceptors were not blocked by cariprazine in the present study. Indeed, cariprazine pretreatment did not result in dampening of the inhibitory action of the α2-adrenoceptor agonist clonidine on NE neurons; this is consistent with its weak or negligible affinity for these receptors as determined by in vitro binding assays (Kiss et al., 2010). It is interesting to note that this lack of effect on α2-adrenergic receptors differs from other medications used to treat psychosis and/or mania (Dremencov et al., 2007; Ghanbari et al., 2009; Oosterhof et al., 2014).

It is important to consider whether the doses of cariprazine used in the present experiments produced plasma levels within the range of those achieved in humans. Because 5-HT2A antagonism is an important feature of this class of medication, both in mood disorders and schizophrenia, the cariprazine concentrations that reversed the effect of the 5-HT2A receptor agonist DOI by cariprazine in the LC were used for comparison with human plasma concentrations. Given that a dose of 1 mg/kg of cariprazine (intravenous) results in a peak plasma level of 240 ng/ml in rats (Gyertyán et al., 2011), it can be extrapolated that the 0.2 mg/kg dose of cariprazine necessary to reverse the suppression of firing by DOI should have produced a level of 48 ng/ml in plasma. This is consistent with the 50 ng/ml plasma level of cariprazine active moieties reported in patients receiving cariprazine at 3 mg/d (Nakamura et al., 2016).

In this study, in agreement with its in vitro affinity, cariprazine showed acute in vivo activity with effective agonism at 5-HT1A receptors and antagonism at 5-HT2A receptors. Agonism at 5-HT1A receptors has been shown to play a key role in the control of mood and cognition (Newman-Tancredi, 2010), while antagonism at 5-HT2A receptors is thought to play a role in modulating the NE system. Hence, it is possible that the activation of 5-HT1A receptors and the blockade of 5-HT2A receptors by cariprazine may contribute to its beneficial therapeutic action seen in major depressive disorder (Durgam et al., 2016a) and bipolar depression (Durgam et al., 2016b).

Acknowledgments

Editorial support for manuscript preparation was provided by Katharine Fang of Prescott Medical Communications Group, Chicago, IL (a contractor of Allergan).

Authorship Contributions

Participated in research design: El Mansari, Kiss, Farrak, Blier. Conducted experiments: Herman, El Mansari. Wrote or contributed to the writing of the manuscript: Herman, El Mansari, Adham, Kiss, Farrak, Blier.
Kenanik T (1987) Agonists, partial agonists, antagonists, inverse agonists and ago-
nist/antagonists? Trends Pharmacol Sci 8:423–428.

Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, Hasnain M,
Jollant F, Levitt AJ, MacQueen GM, et al.; CANMAT Depression Work Group
(2016) Canadian network for mood and anxiety treatments (CANMAT) 2016 clini-
cal guidelines for the management of adults with major depressive disorder: Sec-
tion 3. Pharmacological treatments. Can J Psychiatry 61:540–560.

Kiss B, Horváth A, Nemethy Z, Schmidt E, Laszlovszky I, Bugovics G, Fazekas K,
Hornok K, Orosz S, Gyertyan I, et al. (2010) Cariprazine (RGH-188), a dopamine
D3 receptor-prefering, D3/D2 dopamine receptor antagonist–partial agonist anti-
psychotic candidate: in vitro and neurochemical profile. J Pharmacol Exp Ther 333:
328–340.

Lawler CP, Prioleau C, Lewis MM, Mak C, Jiang D, Schetz JA, Gonzalez AM, Sibley
DR, and Mailman RB (1999) Interactions of the novel antipsychotic aripiprazole
(ÒPC-14597) with dopamine and serotonin receptor subtypes. Neuro-
psychopharmacology 20:612–627.

Li Z, Ichikawa J, Dai J, and Meltzer HY (2004) Aripiprazole, a novel antipsychotic
drug, preferentially increases dopamine release in the prefrontal cortex and hip-
ncampus in rat brain. Eur J Pharmacol 493:75–83.

Maeda K, Sugino H, Akazawa H, Amada N, Shimada J, Futamura T, Yamashita H,
Ito N, McGuade RD, Mørk A, et al. (2014) Brexpiprazole I: in vitro and in vivo
characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp
Ther 350:589–604.

Nakamura T, Kubota T, Iwakai A, Imaida M, Kapás M, and Morio Y (2016) Clinical
pharmacology study of cariprazine (MP-214) in patients with schizophrenia (12-
week treatment). Drug Des Devel Ther 10:327–338.

Nelson JC and Papakostas GI (2009) D3 receptor-preferring, D3/D2 dopamine receptor antagonist–partial agonist anti-
psychotic: in vitro and neurochemical profile. J Pharmacol Exp Ther 333:
328–340.

Newman-Tancredi A (2010) The importance of 5-HT1A receptor agonism in anti-
pyschotic treatment: a meta-analysis of placebo-controlled randomized trials. Am J
Psychiatry 166:880–891.

Newman-Tancredi A (2010) The importance of 5-HT1A receptor agonism in anti-
pyschotic drug action: rationale and perspectives. Curr Opin Invest Drugs 11:
802–812.

O’Ozdemir OA, El Mansari M, and Blier P (2014) Acute effects of brexpiprazole on
serotonin, dopamine, and norepinephrine systems: an in vivo electrophysiological
characterization. J Pharmacol Exp Ther 351:585–595.

Paxinos G and Watson C (2007) The Rat Brain in Stereotaxic Coordinates, 7th ed,
Elsevier Inc, Burlington, MA.

Ranck JB Jr (1975) Behavioral correlates and firing repertoires of neurons in the
dorsal hippocampal formation and septum of unstrained rats, in The Hippo-
campus (Isaacson RL and Pribram KH eds) pp 207–244, Plenum Press, New York.