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Antidepressant response to aripiprazole augmentation associated with enhanced FDOPA utilization in striatum: A preliminary PET study

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ABSTRACT

Several double blind, prospective trials have demonstrated an antidepressant augmentation efficacy of aripiprazole in depressed patients unresponsive to standard antidepressant therapy. Although aripiprazole is now widely used for this indication, and much is known about its receptor-binding properties, the mechanism of its antidepressant augmentation remains ill-defined. In vivo animal studies and in vitro human studies using cloned dopamine dopamine D2 receptors suggest aripiprazole is a partial dopamine agonist; in this preliminary neuroimaging trial, we hypothesized that aripiprazole's antidepressant augmentation efficacy arises from dopamine partial agonist activity. To test this, we assessed the effects of aripiprazole augmentation on the cerebral utilization of 6-[^{18}F]-fluoro-3,4-dihydroxy-L-phenylalanine (FDOPA) using positron emission tomography (PET). Fourteen depressed patients, who had failed 8 weeks of antidepressant therapy with selective serotonin reuptake inhibitors, underwent FDOPA PET scans before and after aripiprazole augmentation; 11 responded to augmentation. Whole brain, voxel-wise comparisons of pre- and post-aripiprazole scans revealed increased FDOPA trapping in the right medial caudate of augmentation responders. An exploratory analysis of depressive symptoms revealed that responders experienced large improvements only in putatively dopaminergic symptoms of lassitude and inability to feel. These preliminary findings suggest that augmentation of antidepressant response by aripiprazole may be associated with potentiation of dopaminergic activity.

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1. Introduction

Three large multi-center trials have reported that the dopamine partial agonist aripiprazole (aripiprazole; Abilify®) is effective in augmenting the response of patients with major depressive disorder (MDD) to oral antidepressant therapy (Berman et al., 2007; Marcus et al., 2008; Berman et al., 2009). All three studies, using identical designs, demonstrated that large subset (ranging from 32 to 47%) of patients who failed to respond to eight weeks of monotherapy, selectively responded to aripiprazole augmentation (as compared with blinded placebo). Data from the first two pivotal trials (Berman et al., 2007; Marcus et al., 2008) led to approval by the United States Food and Drug Administration of aripiprazole for use as an antidepressant augmentation agent in major depressive disorder.

How aripiprazole brings about this antidepressant potentiation is not known, although it clearly binds with high affinity to dopamine D2 and D3 (D2/3) receptor subtypes (Pae et al., 2008). In vivo animal studies suggest that aripiprazole has both dopamine D2, presynaptic agonist (Kikuchi et al., 1995; Semba et al., 1995; Momiyama et al., 1996) and antagonist activities (Kikuchi et al., 1995; Inoue et al., 1996), depending on the assay conditions. The complex pharmacology of aripiprazole may result from variable competition from endogenous dopamine at the same receptors (Burris et al., 2002). The results of studies in vitro in which endogenous dopamine is removed, more consistently indicate aripiprazole to be inherently a D2 partial agonist (Inoue et al., 1996, 1997; Lawler et al., 1999).

Whether aripiprazole functions as a partial agonist in humans is still not known with certainty; however, studies using cloned

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human D2 receptors strongly suggest it has partial activity at D2 receptors. Because multiple factors potentially interfere with assessment of receptor ligand activity (intrinsic receptor activity, receptor density, and signal transduction coupling efficiency (Kenakin, 1997), Burris et al. (2002) conducted a series of studies in vitro using cloned human D2 receptors, designed to control for these factors. Here, binding properties of aripiprazole were consistent with that of a partial agonist. In particular, aripiprazole bound with slightly greater (2 ×) affinity to the G protein-coupled state of D2 receptors (a property of D2 receptor agonists (Lahti et al., 1992)), whereas full agonists have considerably higher affinity (30 ×). Further, aripiprazole also demonstrated affinity to the uncoupled state of the receptor, consistent with an antagonist. Furthermore, treatment of cells with an irreversible antagonist of D2 receptors (*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline or EEDQ) revealed partial agonist properties, as evidenced by the relationship between perturbations in receptor reserve and signal transduction, i.e. cAMP accumulation).

Additional evidence that supports the partial agonist action of aripiprazole includes studies which reveal only a partial inhibition of prolactin release in transformed lactotrophs (Aihara et al., 2004), and low intrinsic efficacy at human D2 receptors expressed in Chinese Hamster Ovary (CHO) cells (Tadori et al., 2005). Further, human [^{11}C]-raclopride PET studies have revealed occupancy exceeding 70% at dopamine D2/3 receptors following a single dose of aripiprazole (Takahata et al., 2012), and exceeding 95% with repeated dosing, while not provoking extrapyramidal side effects (Yokoi et al., 2002), and without the unfavorable subjective experience evoked by antagonist antipsychotic medications (Mizrahi et al., 2009).

In addition to its actions at dopamine D2/3 receptors, aripiprazole is also a D4 partial agonist, as well as a high-affinity partial agonist at serotonin 5HT1A, 5HT2C/5HT7, and 5HT2A/5HT6 receptors (Jordan et al., 2002; Pae et al., 2008); any or all of these receptors might conceivably contribute to the therapeutic effects of aripiprazole.

Multiple lines of evidence support the notion that brain dopamine plays a critical role in MDD (Dunlop and Nemeroff, 2007), primarily through the mesolimbic and mesocortical pathways. The mesocortical pathway, which arises in the midbrain ventral tegmental area and innervates the frontal and temporal cortical region, is implicated in working memory, concentration, and executive function, all of which are frequently disrupted in MDD (Nestler and Carlezon, 2006). Arising in parallel to the mesocortical pathway is the mesolimbic pathway, which sends projections to the ventral striatum (nucleus accumbens), hippocampus, amygdala, cingulate, and prefrontal cortices (among other structures) and is primarily implicated in the maintenance of motivation, hedonic capacity, and reward assessment (Nestler and Carlezon, 2006).

This trial investigated the mechanism of action of aripiprazole augmentation to ineffective treatment of major depressive disorder (MDD) with a selective serotonin reuptake inhibitor (SSRI). Our hypothesis was that efficacious augmentation therapy with aripiprazole occurs in association with potentiation of dopaminergic brain systems. To test this hypothesis, we used positron emission tomography (PET) with the DOPA decarboxylase substrate 6-[^{18}F]-fluoro-3,4-dihydroxy-L-phenylalanine (FDOPA), which has been used extensively for imaging of the presynaptic dopaminergic system in brain. Specific signal in FDOPA-PET studies is derived via the formation of 6-[^{18}F]fluorodopamine in situ and its retention within synaptic vesicles, mainly of dopamine fibers (Kumakura and Cumming, 2009).

Depressed subjects in the present molecular imaging study first underwent an eight week trial of the SSRI escitalopram, along with subject-blind aripiprazole placebo. Those subjects who did not respond to escitalopram plus placebo were recruited to undergo FDOPA-PET scans at escitalopram baseline (just prior to aripiprazole augmentation) and again after six weeks of subject-blind aripiprazole augmentation of escitalopram. Voxel-wise comparisons of FDOPA uptake ratios were then made to search for significant increases in tracer trapping among aripiprazole augmentation responders. Additionally, an exploratory analysis examined whether depressive symptoms that have been a priori identified as dopaminergic (lassitude and inability to feel) demonstrated a greater degree of improvement within the aripiprazole antidepressant augmentation responders (compared with nonresponsers).

2. Methods

2.1. Subjects

All subjects provided written, informed consent approved by the institutional review board at Washington University School of Medicine. Subjects were recruited from radio advertisements. Study inclusion criteria were as follows: (1) history of MDD (met criteria for MDD per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised (American Psychiatric Association, 2000), which was further verified via structured clinical interview with the Mini International Neuropsychiatric Interview (Sheehan et al., 1998); (2) history of non-response to one adequate dose-duration trial of antidepressant therapy; (3) age 18–55 years; and (4) score ≥ 18 on the Hamilton Depression Rating Scale (24-item HDRS; Hamilton, 1967) at baseline. The upper age restriction was included to avoid the potential confound of enhanced washout of FDOPA-derived specific signal in older individuals (Kumakura et al., 2010). Subsequent entry into the aripiprazole augmentation phase of the study required non-response to eight weeks of escitalopram therapy (< 50% change in Montgomery–Åsberg Depression Rating Scale [MADRS] score; Montgomery and Åsberg, 1979) from Baseline to week 8.

Exclusion criteria included the following: (1) history of smoking, due to known effects of smoking on striatal dopamine release (Busto et al., 2009); (2) by DSM-IV TR criteria (American Psychiatric Association, 2000), significant history of active anxiety disorder, since anxiety disorders may significantly affect dopaminergic activity (Schneier et al., 2000); (3) pregnancy/lactation; (4) ability to become pregnant and not using effective contraception; (5) as defined by DSM-IV: organic mental disorders, substance abuse/dependence, schizophrenia, other psychotic disorders, bipolar disorder, and eating disorders; (6) acute suicide risk as judged by the study psychiatrists (i.e., presence of serious suicide intention or plan); and (7) use of any other form of depression treatment.

2.2. Pharmacotherapy and assessment schedule

Subjects were informed that the purpose of the study was to assess the effects of aripiprazole antidepressant augmentation of their standard antidepressant treatment over 16 weeks, and that blinded inititiation of aripiprazole augmentation could occur at any point during the trial. In fact, all subjects received placebo aripiprazole up to week 10. Assessments and treatment phases are outlined in Fig. 1.

2.2.1. Escitalopram monotherapy phase (8 weeks)

Subjects took open-label escitalopram and single-blinded placebo aripiprazole ("placebo 1" in Fig. 1). Escitalopram was selected as the primary treatment because of its generally high effectiveness and lack of significant direct interactions with dopamine transporters or receptors (Owens et al., 2001). Subjects were started on 10 mg per day of oral escitalopram which, if tolerated, was titrated up to 20 mg within the first week and maintained at this dose for the study duration. Subjects whose week 8 MADRS scores declined from baseline by ≥ 50% were considered "responders" and exited the study.

2.2.2. Placebo aripiprazole-only phase (2 weeks)

Escitalopram nonresponders entered a further 2-week phase of escitalopram with placebo aripiprazole ("placebo 2" in Fig. 1), so as to further evaluate for potential placebo response.

2.2.3. Augmentation with aripiprazole (6 weeks)

Subjects entering the single-blind aripiprazole augmentation phase maintained their escitalopram dose and received an initial daily dose of 2 mg of oral aripiprazole. If tolerated, the dose was titrated up to 5 mg at the end of week 11 and to 10 mg at the end of week 12 (maximum study dose). In the event of emergence of akathisia or involuntary movements, the dose was decreased to the previous level.

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