



Dextromethorphan as a potential rapid-acting antidepressant

Edward C. Lauterbach*

Department of Psychiatry and Behavioral Sciences, Mercer University School of Medicine, 1550 College Street, Macon, GA 31201, United States
Department of Internal Medicine, Neurology Section, Mercer University School of Medicine, 1550 College Street, Macon, GA 31201, United States

ARTICLE INFO

Article history:

Received 18 January 2011

Accepted 4 February 2011

ABSTRACT

Dextromethorphan shares pharmacological properties in common with antidepressants and, in particular, ketamine, a drug with demonstrated rapid-acting antidepressant activity. Pharmacodynamic similarities include actions on NMDA, μ opiate, sigma-1, calcium channel, serotonin transporter, and muscarinic sites. Additional unique properties potentially contributory to an antidepressant effect include actions at β , alpha-2, and serotonin1b/d receptors. It is therefore, hypothesized that dextromethorphan may have antidepressant efficacy in bipolar, unipolar, major depression, psychotic, and treatment-resistant depressive disorders, and may display rapid-onset of antidepressant response. An antidepressant response may be associated with a positive family history of alcoholism, prediction of ketamine response, increased AMPA-to-NMDA receptor activity ratio, antidepressant properties in animal models of depression, reward system activation, enhanced erythrocyte magnesium concentration, and correlation with frontal μ receptor binding potential. Clinical trials of dextromethorphan in depressive disorders, especially treatment-resistant depression, now seem warranted.

© 2011 Elsevier Ltd. All rights reserved.

Introduction

Recently, the *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine has been demonstrated to mediate rapid antidepressant action in clinical trials. A growing number of studies evidence the rapid-acting antidepressant effect of ketamine in both unipolar and bipolar depression [1].

A variety of studies have found positive results with single-dose intravenous ketamine in depression, including treatment-resistant bipolar depression in a randomized, placebo-controlled, double-blind, crossover, add-on study [2], treatment-resistant major depression [3] and treatment-resistant major depression with suicidal ideation [4] in an open-label case series (0.5 mg/kg) and randomized, placebo-controlled, double-blind studies [5,6], including one with crossover design [6], of 0.5 mg/kg in subjects with treatment-resistant major depression, and in a variety of case reports. In a study of 0.5 mg/kg i.v. doses given every 2–3 days for a total of 6 doses, an open-label investigation found an 85% reduction in MADRS depression scale scores with only mild side-effects, however, patients usually relapsed several weeks after the final dose [7]. Response to single-dose ketamine may be predicted by a family history of alcohol dependence [8] and increased anterior cingulate activity on a fearful face paradigm [9]. The antidepressant effect of ketamine has also been noted in 70 postoperative patients with depression randomized to anesthetic induction with or without

ketamine, assessed by the Hamilton depression rating scale two days before and one day after surgery [10].

Pharmacodynamic comparisons between the NMDA antagonists dextromethorphan and ketamine suggest the hypothesis that dextromethorphan clinical trials may show similar antidepressant efficacy. A dextromethorphan treatment, dextromethorphan combined with quinidine, has recently been approved by the FDA for pseudobulbar affect, with the quinidine component intended to raise plasma dextromethorphan levels through inhibition of CYP2D6 metabolism.

The hypothesis

It is hypothesized that dextromethorphan has antidepressant activities, is efficacious in the treatment of depressive disorders (including bipolar, unipolar, and treatment-resistant depressive disorders), and produces a rapid antidepressant response.

Evaluation of the hypothesis

Thus far, no study has evaluated dextromethorphan for antidepressant activity, however dextromethorphan has striking pharmacological similarities to ketamine, an effective antidepressant as described above.

Like ketamine [11–13], dextromethorphan is a noncompetitive NMDA receptor antagonist and an agonist at mu (μ) opioid and sigma-1 receptors [14]. Both drugs are also selective μ agonists [15] and block calcium channels [16], serotonin transporters [14,17], and muscarinic receptors [14,18]. Intravenous ketamine

* Tel.: +1 478 745 8531.

E-mail address: eclbgnp@earthlink.net

(0.1 mg/kg) predicted response to oral dextromethorphan in two fibromyalgia studies, with positive predictive values of 64% and 77% and negative predictive values of 73% and 91% [19,20].

There is evidence of a relation between antidepressant activity and these shared properties of dextromethorphan and ketamine.

NMDA receptor antagonist properties

Glutamate may play a key role in the final common pathway of antidepressant action through an increase in the ratio of AMPA/NMDA receptor activity [21,22].

Magnesium regulates the NMDA receptor ion channel [23] and a number of reports correlate depression with hypomagnesemia, with resolution upon normalization of magnesium status, including in treatment resistant depression [24]. Anxiolytic [25] and antidepressant [26] effects of magnesium in mouse models are linked to its action on NMDA receptors. In a rat model of anhedonia, magnesium administration increased reward system activity [27].

Depression is a manifestation of hypomagnesemia [28]. In erythrocytes of patients with major depression, decreased magnesium concentrations correlated with depressive severity, and both amitriptyline and sertraline have been documented to reverse this reduction [27]. Moreover, low levels of magnesium in cerebrospinal fluid and in brain have been documented in treatment-resistant depression [24].

A number of anecdotal reports of rapid depressive response to magnesium can be found in the literature [24,29], including treatment-resistant depression [24]. Intravenous administration of the NMDA antagonist magnesium sulfate dramatically improved depression in a patient with hypomagnesemia in Gitelman's syndrome [30]. In 23 patients with diabetes mellitus type II, major depression, and hypomagnesemia, a randomized trial of magnesium chloride (2.1 ± 0.08 mg/dl) vs. imipramine (1.5 ± 0.07 mg/dl) demonstrated equal antidepressant efficacy of the two treatments [31].

Dextromethorphan has a similar NMDA phencyclidine (PCP) receptor site binding affinity to memantine [14], another drug with preclinical and clinical antidepressant properties [32–34], including rapid-onset antidepressant properties in patients with major depression [34]. PCP itself induces depressive behavior in an animal model [35], and antagonism of this NMDA site may be important in depressive pathophysiology.

Mu receptor agonist properties

Regarding μ receptors and depression, opioid peptides are enriched in affective-related brain regions, serotonin–norepinephrine reuptake inhibiting antidepressants enhance opioid pathway activity, and antidepressant-induced improvements in forced swimming and learned helplessness animal models of depression are reversed by the μ opiate receptor antagonist naloxone [36]. Furthermore, frontal cortical μ binding is elevated in suicide completers [37] and μ binding potential has been correlated with both mood and major depression in women [38]. The μ receptor has also been genetically associated with citalopram response in major depression [39].

Combined NMDA and μ receptor properties

A proper balance of NMDA and μ properties may be requisite for antidepressant activity. Fentanyl 0.2 mg/70 kg i.v. (much higher μ agonist potency but much weaker NMDA antagonist than dextromethorphan), did not improve mood in 15 depressed patients although it increased plasma norepinephrine and cortisol and reduced growth hormone relative to non-depressed controls [40]. It

is possible that a combination of potent μ stimulation with NMDA antagonism is necessary for the alleviation of depression.

Sigma-1 receptor agonist and calcium channel antagonist properties

The sigma-1 receptor is related to major depression pathophysiology [41,42], and to antidepressant response [41] in animal models of depression [43,44] and in psychotic major depression [45,46]. The only case series of calcium channel blocker treatment of major depression revealed a clinically substantial antidepressant activity of nimodipine, with a 63% decline in Hamilton depression scores; all 10 subjects improved, with half achieving full remission [47].

Serotonergic and cholinergic properties

The relation between serotonin transporter blockade and antidepressant activity is well known, especially in regard to selective serotonin reuptake inhibitors. The cholinergic hypothesis of depression has been longstanding, with muscarinic blockade correlating with improvements in Montgomery–Asberg depression ratings [48].

Other monoaminergic antidepressant properties unique to dextromethorphan

Additional properties may distinguish dextromethorphan from ketamine and other NMDA antagonists. Pharmacodynamic comparison of dextromethorphan to the antidepressant drugs amitriptyline and fluoxetine in rat brain showed similar binding profiles for β , α -2, and serotonin1b/d receptors [14], mechanisms that have each been linked to antidepressant activity.

Clinical evaluation of dextromethorphan

A literature search of dextromethorphan in the treatment of depressive disorders proved to be unrevealing. Clinical trials of dextromethorphan now seem warranted, especially for rapid-acting relief of depressive symptoms and treatment-resistant depression.

Consequences of the hypothesis

Experimental confirmation of the hypothesis may demonstrate dextromethorphan's fulfillment of certain predictions: (1) clinically significant antidepressant effects in patients with bipolar and unipolar depressive disorders; (2) clinically significant antidepressant effects in patients with treatment-resistant depression; (3) a rapid-onset of antidepressant response within days of initial administration; (4) response associated with family history of alcoholism; (5) response predicts an antidepressant response to ketamine; (6) response associated with an increase in AMPA/NMDA receptor activity ratio; (7) antidepressant properties in animal models of depression (e.g., forced swimming, learned helplessness) and perhaps anxiety; (8) increased reward system activity in responders in animal models and human patients; (9) increased erythrocyte magnesium concentrations correlating with human antidepressant response; (10) changes in frontal μ binding potential correlating with human antidepressant response; (11) antidepressant and possible antipsychotic therapeutic effect in psychotic depression. Prediction 1 will be the most easily demonstrated, followed by predictions 2, 3, and 11. The other predictions are desirable but not critical to testing the hypothesis.

Evaluation of the hypothesis will further our pharmacodynamic understanding of effective antidepressant treatments. This is particularly true in regard to NMDA, μ , and sigma-1 receptors, NMDA/ μ balance, and AMPA/NMDA activity ratio. In the clinical

arena, it has the potential to avail a treatment for resistant depressions or severe depressions that require rapid relief.

Depressive disorders are a major source of morbidity and cost. The most common of these, major depression, affects up to 20% of the population and imposes a substantial economic burden [49]. In addition, treatment-refractory depression occurs in up to 15% of depressed patients [50]. Therapeutic application of an already-approved drug to these disorders, if effective, can therefore produce significant benefit.

Conflict of interest statement

The author has no perceived direct financial or other conflicts of interest. This work was not supported by any government, corporate, or institutional funding.

References

- [1] Krystal JH. *N*-methyl-D-aspartate glutamate receptor antagonists and the promise of rapid-acting antidepressants. *Arch Gen Psychiatry* 2010;67:1110–1.
- [2] Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* 2010;67:793–802.
- [3] Machado-Vieira R, Yuan P, Brutsche N, et al. Brain-derived neurotrophic factor and initial antidepressant response to an *N*-methyl-D-aspartate antagonist. *J Clin Psychiatry* 2009;70:1662–6.
- [4] Diazgranados N, Ibrahim LA, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an *N*-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry* 2010;71:1605–11.
- [5] Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 2000;47:351–4.
- [6] Zarate Jr CA, Singh JB, Carlson PJ, et al. A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006;63:856–64.
- [7] van het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry* 2010;67:139–45.
- [8] Phelps LE, Brutsche N, Moral JR, et al. Family history of alcohol dependence and initial antidepressant response to an *N*-methyl-D-aspartate antagonist. *Biol Psychiatry* 2009;65:181–4.
- [9] Salvatore G, Cornwall BR, Colon-Rosario V, et al. Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. *Biol Psychiatry* 2009;65:289–95.
- [10] Kudoh A, Takahira Y, Katagai H, Takazawa T. Small-dose ketamine improves the postoperative state of depressed patients. *Anesth Analg* 2002;95:114–8.
- [11] Harrison NL, Simmonds MA. Quantitative studies on some antagonists of *N*-methyl-D-aspartate in slices of rat cerebral cortex. *Br J Pharmacol* 1985;84:381–91.
- [12] Hirota K, Sikand KS, Lambert DG. Interaction of ketamine with mu2 opioid receptors in SH-SY5Y human neuroblastoma cells. *J Anesth* 1999;13:107–9.
- [13] Narita M, Yoshizawa K, Aoki K, Takagi M, Miyatake M, Suzuki T. A putative sigma1 receptor antagonist NE-100 attenuates the discriminative stimulus effects of ketamine in rats. *Addict Biol* 2001;6:373–6.
- [14] Werling LL, Keller A, Frank JG, Nuwayhid SJ. A comparison of the binding profiles of dextromethorphan, memantine, fluoxetine, and amitriptyline: treatment of involuntary emotional expression disorder. *Exp Neurol* 2007;207:248–57.
- [15] Baker AK, Hoffmann VL, Meert TF. Dextromethorphan and ketamine potentiate the antinociceptive effects of mu- but not delta- or kappa-opioid agonists in a mouse model of acute pain. *Pharmacol Biochem Behav* 2002;74:73–86.
- [16] Kamel IR, Wendling WW, Chen D, Wendling KS, Harakal C, Carlsson C. *N*-methyl-D-aspartate (NMDA) antagonists-(+)-ketamine, dextrophan, and dextromethorphan-act as calcium antagonists on bovine cerebral arteries. *J Neurosurg Anesthesiol* 2008;20:241–8.
- [17] Martin DC, Introna RP, Aronstam RS. Inhibition of neuronal 5-HT uptake by ketamine, but not halothane, involves disruption of substrate recognition by the transporter. *Neurosci Lett* 1990;112:99–103.
- [18] Durieux ME. Inhibition by ketamine of muscarinic acetylcholine receptor function. *Anesth Analg* 1995;81:57–62.
- [19] Cohen SP, Chang AS, Larkin T, Mao J. The intravenous ketamine test: a predictive response tool for oral dextromethorphan treatment in neuropathic pain. *Anesth Analg* 2004;99:1753–9.
- [20] Cohen SP, Verdolin MH, Chang AS, Kurihara C, Morlando BJ, Mao J. The intravenous ketamine test predicts subsequent response to an oral dextromethorphan treatment regimen in fibromyalgia patients. *J Pain* 2006;7:391–8.
- [21] Maeng S, Zarate Jr CA, Du J, et al. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry* 2008;63:349–52.
- [22] Maeng S, Zarate Jr CA. The role of glutamate in mood disorders: results from the ketamine in major depression study and the presumed cellular mechanism underlying its antidepressant effects. *Curr Psychiatry Rep* 2007;9:467–74.
- [23] Danyasz W, Parsons CG. The NMDA receptor antagonist memantine as a symptomatological and neuroprotective treatment for Alzheimer's disease: preclinical evidence. *Int J Geriatr Psychiatry* 2003;18(Suppl. 1):S23–32.
- [24] Eby 3rd GA, Eby KL. Magnesium for treatment-resistant depression: a review and hypothesis. *Med Hypotheses* 2010;74:649–60.
- [25] Poleszak E, Wlaz P, Wróbel A, Fidecka S, Nowak G. NMDA/glutamate mechanism of magnesium-induced anxiolytic-like behavior in mice. *Pharmacol Rep* 2008;60:655–63.
- [26] Poleszak E, Wlaz P, Kedzierska E, et al. NMDA/glutamate mechanism of antidepressant-like action of magnesium in forced swim test in mice. *Pharmacol Biochem Behav* 2007;88:158–64.
- [27] Nechifor M. Magnesium in major depression. *Magnes Res* 2009;22:163S–6S.
- [28] Berkelhammer C, Bear RA. A clinical approach to common electrolyte problems: 4. Hypomagnesemia. *Can Med Assoc J* 1985;132:360–8.
- [29] Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. *Med Hypotheses* 2006;67:362–70.
- [30] Enya M, Kanoh Y, Mune T, et al. Depressive state and paresthesia dramatically improved by intravenous MgSO₄ in Gitelman's syndrome. *Intern Med* 2004;43:410–4.
- [31] Barragán-Rodríguez L, Rodríguez-Morán M, Guerrero-Romero F. Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial. *Magnes Res* 2008;21:218–23.
- [32] Réus GZ, Stringari RB, Kirsch TR, et al. Neurochemical and behavioural effects of acute and chronic memantine administration in rats: Further support for NMDA as a new pharmacological target for the treatment of depression? *Brain Res Bull* 2010;81:585–9.
- [33] Muhonen LH, Lönnqvist J, Juva K, Alho H. Double-blind, randomized comparison of memantine and escitalopram for the treatment of major depressive disorder comorbid with alcohol dependence. *J Clin Psychiatry* 2008;69:392–9.
- [34] Ferguson JM, Shingleton RN. An open-label, flexible-dose study of memantine in major depressive disorder. *Clin Neuropharmacol* 2007;30:136–44.
- [35] Noda Y, Yamada K, Furukawa H, Nabeshima T. Enhancement of immobility in a forced swimming test by subacute or repeated treatment with phencyclidine: a new model of schizophrenia. *Br J Pharmacol* 1995;116:2531–7.
- [36] Berrocoso E, Sánchez-Blázquez P, Garzón J, Mico JA. Opiates as antidepressants. *Curr Pharm Des* 2009;15:1612–22.
- [37] Escríbá PV, Ozaita A, García-Sevilla JA. Increased mRNA expression of alpha2A-adrenergic receptors, serotonin receptors and mu-opioid receptors in the brains of suicide victims. *Neuropsychopharmacology* 2004;29:1512–21.
- [38] Kennedy SE, Koeppe RA, Young EA, Zubieta JK. Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. *Arch Gen Psychiatry* 2006;63:1199–208.
- [39] Garriock HA, Tanowitz M, Kraft JB, et al. Association of mu-opioid receptor variants and response to citalopram treatment in major depressive disorder. *Am J Psychiatry* 2010;167:565–73.
- [40] Matussek N, Hoehle M. Investigations with the specific mu-opiate receptor agonist fentanyl in depressive patients: growth hormone, prolactin, cortisol, noradrenaline and euphoric responses. *Neuropsychobiology* 1989;21:1–8.
- [41] Kulkarni SK, Dhir A. Sigma-1 receptors in major depression and anxiety. *Expert Rev Neurother* 2009;9:1021–34.
- [42] Kishi T, Yoshimura R, Okochi T, et al. Association analysis of SIGMAR1 with major depressive disorder and SSRI response. *Neuropharmacology* 2010;58:1168–73.
- [43] Urani A, Roman FJ, Phan VL, Su TP, Maurice T. The antidepressant-like effect induced by sigma(1)-receptor agonists and neuroactive steroids in mice submitted to the forced swimming test. *J Pharmacol Exp Ther* 2001;298:1269–79.
- [44] Hindmarch I, Hashimoto K. Cognition and depression: the effects of fluvoxamine, a sigma-1 receptor agonist, reconsidered. *Hum Psychopharmacol* 2010;25:193–200.
- [45] Stahl SM. Antidepressant treatment of psychotic major depression: potential role of the sigma receptor. *CNS Spectr* 2005;10:319–23.
- [46] Kishimoto A, Todani A, Miura J, Kitagaki T, Hashimoto K. The opposite effects of fluvoxamine and sertraline in the treatment of psychotic major depression: a case report. *Ann Gen Psychiatry* 2010;9:23.
- [47] Walden J, Fritze J, Van Calker D, Berger M, Grunze H. A calcium antagonist for the treatment of depressive episodes: single case reports. *J Psychiatr Res* 1995;29:71–6.
- [48] Furey ML, Khanna A, Hoffman EM, Drevets WC. Scopolamine produces larger antidepressant and anti-anxiety effects in women than in men. *Neuropsychopharmacology* 2010;35:2479–88.
- [49] Patten SB. Recall bias and major depression lifetime prevalence. *Soc Psychiatry Psychiatr Epidemiol* 2003;38:290–6.
- [50] Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can J Psychiatry* 2007;52:46–54.