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Research article

Deuterated (d6)-dextromethorphan elicits antidepressant-like effects in mice

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ABSTRACT

The over-the-counter antitussive dextromethorphan (DM) may have rapid antidepressant actions based on its overlapping pharmacology with ketamine, which has shown fast antidepressant effects but whose widespread use remains limited by problematic side effects. We have previously shown that DM produces antidepressant-like effects in the forced swim test (FST) and tail suspension test (TST) that are mediated in part through α-amino-3-hydroxy-5-methyl-4-isoxazole propionic (AMPA) and sigma-1 receptors, two protein targets associated with a faster onset of antidepressant efficacy. To utilize DM clinically, however, a major challenge that must be addressed is its rapid first-pass metabolism. Two strategies to inhibit metabolism of DM and maintain stable therapeutic blood levels are 1) chemically modifying DM and 2) adding quinidine, an inhibitor of the primary metabolizer of DM, the cytochrome P450 (CYP) 2D6 enzyme. The purpose of this study was to determine if modified DM (deuterated (d6)-DM) elicits antidepressant-like effects and if AMPA and sigma-1 receptors are involved. Furthermore, d6-DM was tested in conjunction with quinidine to determine if further slowing the metabolism of d6-DM affects its antidepressant-like actions. In the FST and TST, d6-DM produced antidepressant-like effects. Upon further investigation in the FST, the most validated animal model for predicting antidepressant efficacy, d6-DM produced antidepressant-like effects both in the absence and presence of quinidine. However, pretreatment with neither an AMPA receptor antagonist (NBQX) nor sigma-1 receptor antagonists (BD1063, BD1047) significantly attenuated the antidepressant-like effects. The data suggest d6-DM has antidepressant-like effects, though it may be recruiting different molecular targets and/or acting through a different mix or ratio of metabolites from regular DM.

1. Introduction

Major depression is one of the most common psychiatric disorders, affecting an estimated 350 million people worldwide, including > 18 million American adults in a given year (World Health Organization, 2017; Valenstein et al., 2001). It is defined by the occurrence of at least one major depressive episode, but most patients will experience recurrent episodes or chronic illness (Mueller and Leon, 1996). In 2000, in the US alone, indirect costs of depression accounted for more than $50 billion, whereas direct costs were $26 billion (Wade and Haring, 2010). Despite advances in pharmaceutical antidepressant therapy, it still takes several weeks before approved medications are effective and about 30% of patients do not respond, leaving them particularly at risk for self-harm (Berton and Nestler, 2006; Schlaepfer et al., 2012).

A major breakthrough in the treatment of depression came in 2000 with the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine reported as a fast acting antidepressant drug (Berman et al., 2000). Since then, evidence supporting this seminal finding has accumulated, but the widespread use of ketamine remains limited by its problematic side effect profile which includes cardiovascular effects, perceptual disturbances, confusion, and a short lived "high" (Fond et al., 2014; McGirr et al., 2015; Aan Het Rot et al., 2012). In the search for alternatives with a more favorable safety profile, the over-the-counter antitussive dextromethorphan (DM) has been postulated to have fast acting antidepressant activity based on pharmacodynamics similarities to ketamine (Lauterbach, 2012; Stahl, 2013). In preclinical studies, DM

Abbreviations: 5-HT, serotonin; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BD1047, (*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(dimethylamino)ethylamine dihydrobromide); BD1063, (1-[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine dihydrochloride); CYP, cytochrome P450; DM, dextromethorphan; d6-DM, deuterated dextromethorphan; FST, forced swim test; i.p., intraperitoneal; NBQX, 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide; NMDA, *N*-methyl-D-aspartate; PBA, pseudobulbar affect; OFT, open field test; TST, tail suspension test

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was recently shown to exert antidepressant-like effects in mice in the forced swim test (FST) (Nguyen et al., 2014) and tail suspension test (TST) (Nguyen and Matsumoto, 2015), two of the most widely used animal models for predicting antidepressant efficacy (Nestler et al., 2002; Cryan and Holmes, 2005; Cryan et al., 2005; McArthur and Borsini, 2006). Evidence involving pharmacological antagonists also suggests that α-amino-3-hydroxy-5-methyl-4-isoxazole propionic (AMPA) (Nguyen and Matsumoto, 2015) and sigma-1 receptors (Nguyen et al., 2014) played significant roles in mediating the antidepressant-like behaviors of DM.

Both AMPA and sigma-1 receptors have been shown to mediate antidepressant actions, including fast acting effects. With regard to AMPA receptors, the glutamatergic system in general has been increasingly implicated in the pathogenesis and pharmacotherapy of depression (Niciu et al., 2013; Freudenberg et al., 2015), and many different classes of antidepressant drugs modulate AMPA receptor function and expression in particular (Bleakman et al., 2007). AMPA potentiators, which increase receptor function by altering receptor kinetics (e.g., decrease receptor desensitization or deactivation), and AMPA itself promote antidepressant-like effects on their own or in combination with other antidepressant drugs (Li et al., 2001; Knapp et al., 2002; Farley et al., 2010; Andreasen et al., 2015). In contrast, AMPA receptor antagonists prevent the antidepressant-like effects of fast acting antidepressants such as ketamine (Koike et al., 2011; Maeng et al., 2008; Autry et al., 2011; Fukumoto et al., 2016; Zanos et al., 2016) and the more recently discovered scopolamine (Voleti et al., 2013), suggesting that AMPA receptors may be important particularly for fast acting antidepressant effects. With regard to sigma-1 receptors, many antidepressant drugs interact with these proteins, and selective sigma-1 agonists can elicit antidepressant-like effects in both laboratory animals and humans (Fishback et al., 2010). Specifically related to fast acting effects, selective sigma-1 agonists have been shown to enhance the firing of serotonergic neurons in the dorsal raphe of rats after only two days of treatment, compared to the two weeks that are typical of conventional antidepressant drugs (Bermack and Debonnel, 2001; Lucas et al., 2008). Together, the data suggests that AMPA or sigma-1 receptors can work independently and/or together with other pathways (e.g., monoaminergic systems) to produce a more rapid onset of antidepressant actions, and that DM, by utilizing these mechanisms, may produce faster acting effects in human populations than conventional antidepressant drugs.

In order for DM to be used in depressed patients, one major challenge that must be overcome is its substantial first-pass metabolism. DM is rapidly metabolized primarily by cytochrome P450 (CYP) 2D6 into its major metabolite dextrorphan (Schmid et al., 1985), decreasing its bioavailability and potential antidepressant efficacy. Moreover, increased exposure to dextrorphan, a more potent NMDA receptor antagonist than DM itself, increases the risk for phencyclidine (PCP)-like psychotomimetic effects seen with high dose DM (Miller, 2011). Two approaches to extend the half-life of DM include 1) adding an inhibitor of CYP2D6, such as quinidine, and 2) chemically modifying DM to inhibit its metabolism. The first strategy has resulted in a combination drug that is approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of pseudobulbar affect (PBA). In addition, treatment with DM/quinidine in depressed patients with treatment-resistant bipolar disorder has been reported to improve mood within 1–2 days in some patients (Kelly and Lieberman, 2014). More recently, a prospective, open-label study of DM/quinidine found that doses up to 45/10 mg every 12 h were well-tolerated and associated with efficacy in patients with treatment-resistant unipolar depression (Murrough et al., 2017). Moreover, a case report showed DM as add-on therapy to the antidepressant and strong CYP2D6 inhibitor bupropion XL produced rapid-acting antidepressant effects within 48 h in treatment-resistant depression (Lauterbach, 2016). These clinical reports support the use of DM in combination with CYP2D6 inhibition. Ideally, because patients may already be taking drugs with strong CYP2D6 inhibition as shown in the case report (Lauterbach, 2016), the latter strategy of chemically modifying DM may prove useful to minimizing drug interactions.

The present study therefore focuses on the second strategy, working with a deuterium (d6)-enriched DM. Deuterium is a naturally occurring isotope. It is one of two stable isotopes of hydrogen which contains one proton and one neutron in the nucleus, in contrast to the lighter and more common isotype, protium, which has no neutron (Gant, 2014). Deuterium can make stronger chemical bonds than hydrogen; when this particular structural modification is made to functional groups commonly degraded during metabolism, the modified compound may have enhanced metabolic stability and hence a longer half-life (Gant, 2014).

Using the FST and TST, the two most validated behavioral assays for assessing antidepressant potential (Nestler et al., 2002; Cryan and Holmes, 2005; Cryan et al., 2005; McArthur and Borsini, 2006), d6-DM was evaluated for antidepressant-like effects. In both tests, the conventional antidepressant imipramine was used as the positive control. Next, to better characterize the antidepressant-like effects of d6-DM, all subsequent studies were carried out in the FST, the more validated of the two behavioral assays (Nestler et al., 2002; Cryan and Holmes, 2005; McArthur and Borsini, 2006). As AMPA and sigma-1 receptors have been implicated in mediating the antidepressant-like actions of regular DM (Nguyen and Matsumoto, 2015; Nguyen et al., 2014), an AMPA receptor antagonist (NBQX) and two sigma-1 antagonists (BD1063 and BD1047) were also evaluated in conjunction with d6-DM to determine the involvement of these two receptors in the antidepressant-like effects of d6-DM. Finally, because the deuteration may only partially reduce the formation of metabolites, d6-DM was also tested in combination with quinidine to determine if the addition of quinidine may improve its antidepressant-like effects.

2. Materials and methods

2.1. Animals

Male, Swiss Webster mice (24–28 g; Harlan, Frederick, MD) were housed with water and food ad libitum, with a 12:12 h light-dark cycle. They were housed in groups of five for at least one week prior to initiation of experiments. For each experimental group, ten mice were used. All procedures were conducted in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The protocol was approved by the Institutional Animal Care and Use Committee at West Virginia University (Morgantown, WV), and all efforts were made to minimize suffering.

2.2. Drugs and chemicals

d6-DM and quinidine sulfate were provided by Avanir Pharmaceuticals, Inc. (Aliso Viejo, CA). Imipramine hydrochloride was purchased from Sigma-Aldrich (St. Louis, MO). NBQX (2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide disodium salt), BD1063 (1-[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine dihydrochloride) and BD1047 (*N*-[2-(3,4-dichlorophenyl)ethyl]-*N*-methyl-2-(dimethylamino)ethylamine dihydrobromide) were purchased from Tocris (Ellisville, MO). All compounds were dissolved in sterile saline (Teknova, Hollister, CA). Mice received intraperitoneal (i.p.) injections of saline or drug solutions at a volume of 10 ml/kg of body weight after acclimating to the open field testing chambers, 30 min prior to the FST or TST. Pretreatment with NBQX, BD1063 or BD1047 was administered 15 min prior to d6-DM. The selected doses and schedules used for the d6-DM were approved by Avanir Pharmaceuticals, Inc. prior to providing the compound. The dosing schedules used for imipramine and NBQX were the same as recently used and reported by our lab for testing with regular DM (Nguyen and Matsumoto, 2015; Nguyen et al., 2014), and consistent with available