CNS Spectrums (2013), **18**, 225–227.
doi:10.1017/S109285291300062X

BRAINSTORMS—Clinical Neuroscience Update

Mechanism of action of dextromethorphan/quinidine: comparison with ketamine

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ISSUE:

Reports of rapid-onset but short-duration antidepressant effects in patients with treatment-resistant mood disorders after intravenous administration of ketamine have prompted efforts to find an agent with ketamine's properties that can be administered orally in repeated doses in order to sustain that action. One candidate for this is dextromethorphan, and here the pharmacologic mechanism of action is compared and contrasted with that of ketamine.

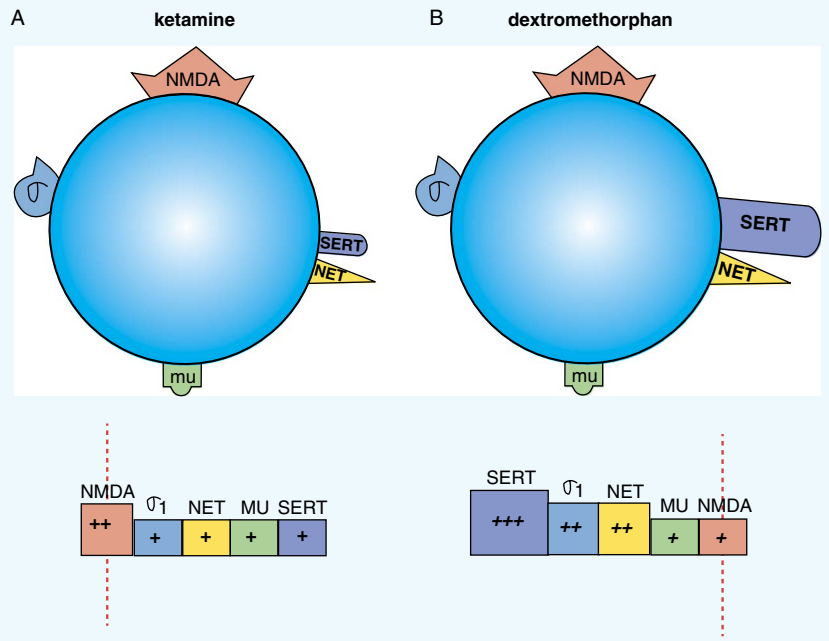
Take-Home Points

- Dextromethorphan binds to several neurotransmitter receptors, notably and in rank order, to the serotonin transporter > the sigma 1 receptor = norepinephrine transporter > the NMDA (N-methyl-d-glutamate) receptor = mu opiate receptor.
- Ketamine binds to these same receptors, but in a different rank order, namely to the NMDA receptor > the sigma 1 receptor = serotonin transporter = mu opiate receptor = norepinephrine transporter. Thus there is considerable overlap between the binding properties of these 2 agents but also differences in the relative order of affinity for these same receptors.
- Dextromethorphan's central nervous system bioavailability can be significantly enhanced when administered orally in combination with a low dose of the cytochrome P450 inhibitor quinidine.
- Dextromethorphan/quinidine combination is approved for the condition of labile affect, known as "pseudobulbar affect," which can afflict certain patients having a wide variety of neurological disorders from mild traumatic brain injury to dementia to multiple sclerosis to amyotrophic lateral sclerosis (ALS) and others.
- Given dextromethorphan's pharmacologic mechanism of action, it is theoretically possible that high doses of dextromethorphan/quinidine could be an effective treatment for various states of affective dysregulation, including those improved by ketamine.

Dextromethorphan was first developed as 1 of the 2 enantiomers of methorphan, with levomethorphan characterized as a low potency opiate analgesic pro-drug and dextromethorphan as an antitussive (cough suppressant) at low doses and dissociative agent at high doses. As dextromethorphan is a substrate of the cytochrome P450 enzyme 2D6 and is rapidly metabolized, oral administration of dextromethorphan by itself leads to rapid and unsustained peak levels of drug with a short duration of action.[1] Oral administration of dextromethorphan alone is fully adequate for rapid-onset, short-duration antitussive actions and that is how it is dosed in various cough suppressants. However, oral administration of dextromethorphan alone does not lead to the sustained levels needed to substantially occupy neurotransmitter receptors in the brain without the need for frequent administration and high-peak doses associated with dissociative side effects.

To solve this problem, dextromethorphan was reformulated in combination with a low dose of the cytochrome P450 2D6 inhibitor quinidine in order to

Figure 1. Comparison of the pharmacologic properties of dextromethorphan and ketamine.



attain high degrees of continuous occupancy of brain receptors without frequent dosing and without peak dose dissociative side effects.[1–3] Specifically, combined with a low dose of the 2D6 inhibitor quinidine, dextromethorphan is converted into a twice-a-day formulation with over 20 times the therapeutic exposure to dextromethorphan levels with quinidine compared to dextromethorphan alone.[1–3] This drug combination also largely avoids the high peak levels of drug that can cause dissociative reactions, yet provides the drug levels necessary for consistent receptor occupancy over time. Dextromethorphan/quinidine is the formulation of dextromethorphan that is approved for treating pseudobulbar affect (PBA) secondary to numerous neurological conditions and is characterized by involuntary, sudden, and frequent episodes of laughing or crying that are typically out of proportion or incongruent with the underlying emotional state.[1–3]

Pharmacologic Mechanism of Action of Dextromethorphan

The pharmacologic actions of dextromethorphan are shown in Figure 1B.[1,4,5] Although much of the older literature emphasizes the weak mu opiate binding properties of dextromethorphan in order to explain its classical antitussive effects, the modern literature emphasizes the more potent sigma 1 actions of dextromethorphan.[2,3] Both of these pharmacologic formulations ignore the potent serotonin reuptake binding properties of dextromethorphan (which is why it is contraindicated with MAO inhibitors), as well as the norepinephrine binding properties and weak NMDA binding properties of dextromethorphan (Figure 1B).[4,5] Obviously, the portfolio of receptors recruited by dextromethorphan and the degree of occupancy of each receptor by this agent depend upon the concentration of dextromethorphan in the brain, which at therapeutic doses for PBA would be predicted to occupy substantial numbers of the receptors for which dextromethorphan has lower affinity and to saturate the receptors for which dextromethorphan has higher affinity. Which receptor or combination of receptors mediate(s) the therapeutic action of dextromethorphan in PBA is unknown, but some theories suggest it might be a combination of the serotonin transporter (some antidepressants improve PBA), the sigma 1 receptor, and the NMDA receptor (since dextromethorphan/quinidine appears to have more robust and sustained effects in PBA than antidepressants).[5]

Comparison of Pharmacologic Actions of Dextromethorphan and Ketamine

A side-by-side comparison of dextromethorphan and ketamine and their principle pharmacologic mechanisms of action are shown in Figure 1 (compare 1A with 1B).[1,4,5]

The mechanism of action of ketamine was also presented in a previous Brainstorms feature.[6] For ketamine, the current literature tends to characterize its actions only as an NMDA antagonist,[7,8] ignoring the 4 other known binding properties shown in Figure 1A, especially ignoring the sigma 1 and serotonin transporter binding.[6] Sigma 1 receptor actions remain somewhat elusive and have been reviewed elsewhere.[9,10] It may be that the only pharmacologic action relevant to ketamine's effects in mood disorders is its NMDA antagonist properties, but it is also possible that other receptors may be involved, since a proportion of them are occupied by ketamine simultaneously with NMDA receptors. Without the availability of selective agents for testing, it will be difficult to determine which receptor or receptors mediate the mechanism of action of ketamine in mood disorders. However, it is interesting to note that ketamine and dextromethophan both share actions at the same 5 neurotransmitter receptors, and if one wished to study an agent with NMDA antagonist properties that is orally bioavailable while simultaneously binding to all 5 receptors, a high dose of dextromethorphan/quinidine has a certain amount of theoretical appeal. Anecdotal evidence from case reports suggests that dextromethorphan/quinidine may have a role in treating the aggression, anger, and mood lability in a number of conditions, ranging from mild traumatic brain injury comorbid with posttraumatic stress disorder to treatment-resistant mood disorders. Further testing is clearly warranted.

The pharmacologic properties of dextromethorphan are represented in Figure 1B and those of ketamine are represented in Figure 1A. The binding properties of both are represented graphically and semiquantitatively. Each drug is shown as a blue sphere, with its most potent binding properties depicted along the outer edge of the sphere. Additionally, each drug has a series of colored boxes associated with it. Each colored box represents a different binding property, and binding affinity is indicated by the size of the box and the number of plus signs. Within the colored box series for each drug, larger boxes with more plus signs (positioned to the left) represent higher binding affinity, while smaller boxes with fewer plus signs (positioned to the right) represent lower binding affinity. The series of boxes associated with each drug are arranged such that the size and positioning of a box reflect the binding potency for a particular receptor. The vertical dotted line cuts through the binding affinity for the NMDA receptor, theoretically the target for mood disorders and affective dysregulation. More potent binding affinities are shown to the left, and less potent are shown to the right for each drug. All binding properties are based on the mean values of published Ki data.[5] This semiquantitative depiction provides a quick visual reference of how much affinity a particular drug binds to a particular receptor, and also allows for easy visual comparison of the 2 drugs' binding properties.

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