

Mechanism of Action of α_{2A} -Adrenergic Agonists in Attention-Deficit/Hyperactivity Disorder With or Without Oppositional Symptoms

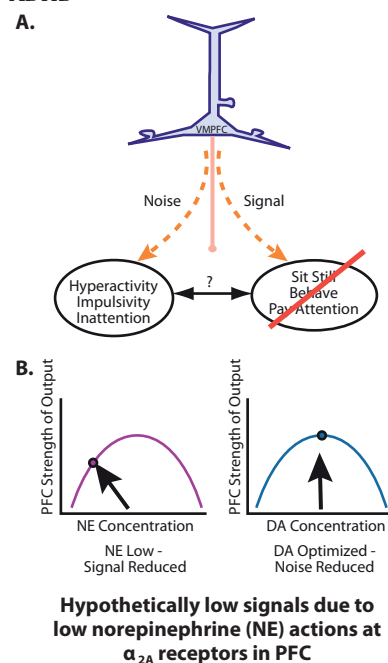
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Issue: α_{2A} -Adrenergic agonists hypothetically increase the strength of signals in prefrontal cortex (PFC), enhancing the efficiency of information processing at pyramidal neurons and resulting in the improvement of symptoms in attention-deficit/hyperactivity disorder (ADHD), including oppositional symptoms.

TAKE-HOME POINTS

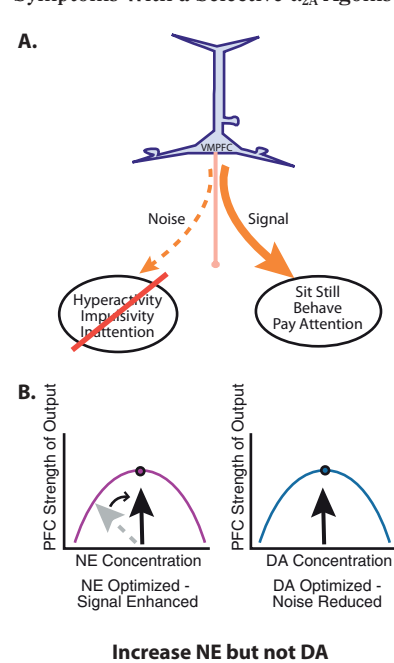
- ◆ A novel nonstimulant medication, guanfacine XR acts selectively at α_{2A} -adrenergic receptors.
- ◆ Stimulation of α_{2A} receptors enhances key signal inputs to pyramidal neurons in prefrontal cortex.
- ◆ Theoretically, enhancing key glutamate signals can reduce not only classical ADHD symptoms, such as hyperactivity, inattention, and impulsivity, but also oppositional symptoms.
- ◆ Guanfacine XR is an approved first-line treatment for classical ADHD symptoms and may also prove to be useful as an augmenting agent to stimulants for treatment-resistant ADHD, including the often difficult to treat oppositional symptoms associated with this disorder.

Figure 1. Classical Childhood-Onset ADHD



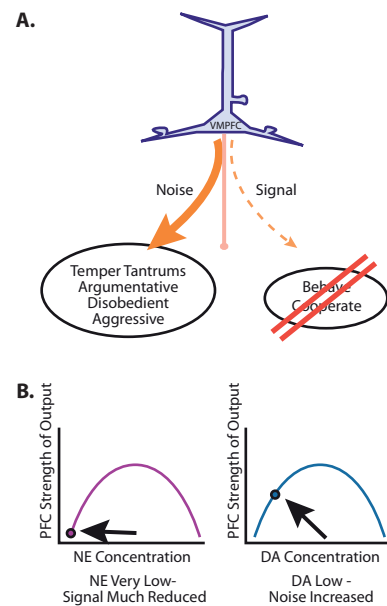
- A: Scrambled signals, stemming from 2 common types of neurotransmitter dysregulation,¹⁻⁶ can become lost in background noise and result in the classical symptoms of ADHD. The clinical outcomes linked to these problems in PFC regulation in children are hyperactivity, impulsivity, and inattention and, in adults, inattention especially.¹⁻⁶
- B: The symptoms of ADHD in some patients may be hypothetically due to low levels of NE in PFC, even when adequate dopamine (DA) levels are present,¹⁻⁵ or to low levels of both NE and DA in PFC¹⁻⁵ (displayed in the last edition of BRAINSTORMS⁹).

Figure 2. Treatment of Classical ADHD Symptoms With a Selective α_{2A} Agonist



- A: In cases where NE concentrations are low, a selective α_{2A} agonist such as guanfacine XR would theoretically "tune" the system, activating α_{2A} -mediated NE actions selectively and thereby relieving the symptoms of ADHD.¹⁻⁹
- B: NE actions are enhanced, but DA actions are not.¹⁻⁷ Other α_2 agonists would have similar stimulating effects at α_{2A} receptors, but can also have undesired effects at other receptors. For example, clonidine has additional and possibly undesired actions at α_{2B} and α_{2C} receptors.^{3,4} Atomoxetine and stimulants (eg, methylphenidate and amphetamine) stimulate all NE receptors: α_{2A} , α_{2B} , and α_{2C} ; α_1 and its subtypes; and β and its subtypes.^{3,4} These same agents also raise DA levels and thus stimulate all DA receptor subtypes as well.^{3,4} For patients in whom nonselective actions at all NE and DA receptors would be undesirable, due to the need to selectively raise only NE and not DA, a selective α_{2A} agonist such as guanfacine XR may offer the best solution.⁴⁻⁹

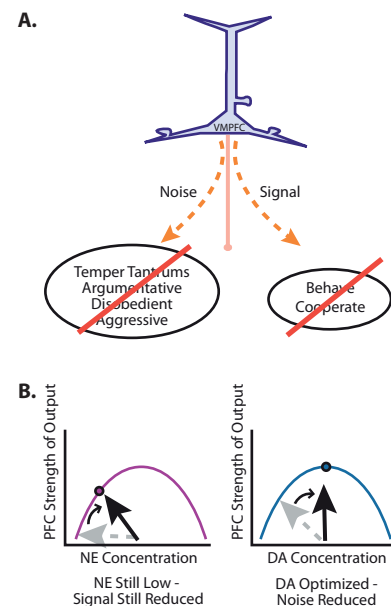
Figure 3. ADHD and Oppositional Symptoms



Hypothetically very low signals due to very low NE and low DA in ventromedial prefrontal cortex (VMPFC)

- A: Patients suffering from ADHD who also have oppositional symptoms can be argumentative, disobedient, and aggressive and exhibit temper tantrums.^{3,4}
- B: Oppositional behaviors may be linked to very low levels of NE and low levels of DA in VMPFC, thus leading to a much reduced signal and increased noise.^{3,4}

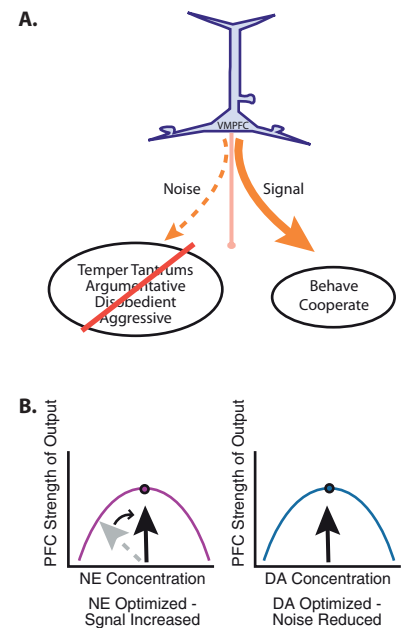
Figure 4. Stimulant Treatment of ADHD and Oppositional Symptoms



Increase NE somewhat and increase DA

- A: While treatment with a stimulant may improve some symptoms of ADHD—with a reduction of inattention, impulsivity, and hyperactivity—in many patients, oppositional symptoms can be very difficult to treat completely.^{3,4}
- B: Hypothetically, the stimulant may have corrected the DA deficiency but only some of the NE deficiency.^{3,4}

Figure 5. Stimulant Augmented With a Selective α_{2A} Agonist for Treatment of ADHD and Oppositional Symptoms



Increase NE and DA

- A: In situations where stimulants improve some but not all symptoms of ADHD, with residual oppositional symptoms, augmentation of a stimulant with a selective α_{2A} -adrenergic agonist such as guanfacine XR may provide an additional selective boost to the NE system at α_{2A} receptors, and resolve more completely these residual oppositional behaviors.^{3,4}
- B: The stimulant increases the DA and NE, while the selective α_{2A} -adrenergic agonist boosts the NE concentration to therapeutic levels.

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