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

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**Issue:** $\alpha_{2A}$-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 $\alpha_{2A}$-adrenergic receptors.
- Stimulation of $\alpha_{2A}$ 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, 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.

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, or to low levels of both NE and DA in PFC.

**Figure 2. Treatment of Classical ADHD Symptoms With a Selective $\alpha_{2A}$ Agonist**

A. NE actions are enhanced, but DA actions are not.

B. Other $\alpha$ agonists would have similar stimulating effects at $\alpha_{2A}$ receptors, but can also have undesired effects at other receptors. For example, clonidine has additional and possibly undesired actions at $\alpha_{2B}$ and $\alpha_{2C}$ receptors. Atomoxetine and stimulants (e.g., methylphenidate and amphetamine) stimulate all NE receptors: $\alpha_{1A}, \alpha_{1B}$, and $\alpha_{1C}$; $\alpha$ and its subtypes; and $\beta$ and its subtypes. These same agents also raise DA levels and thus stimulate all DA receptor subtypes as well. 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 $\alpha_{2A}$ agonist such as guanfacine XR may offer the best solution.
Figure 3. ADHD and Oppositional Symptoms

A. Patients suffering from ADHD who also have oppositional symptoms can be argumentative, disobedient, and aggressive and exhibit temper tantrums.1,4

B. Oppositional behaviors may be linked to very low levels of NE and low levels of DA in ventromedial prefrontal cortex (VMPFC), leading to a much reduced signal and increased noise.1,4

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

A. Temper Tantrums Argumentative Disobedient Aggressive

B. NE Concentration NE Very Low - Signal Much Reduced

DA Concentration DA Low - Noise Increased

Figure 4. Stimulant Treatment of ADHD and Oppositional Symptoms

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

Increase NE somewhat and increase 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 α2-adrenergic agonist such as guanfacine XR may provide an additional selective boost to the NE system at α2A receptors, and resolve more completely these residual oppositional behaviors.3,4

B. The stimulant increases the DA and NE, while the selective α2-adrenergic agonist boosts the NE concentration to therapeutic levels.

Figure 5. Stimulant Augmented With a Selective α2A Agonist for Treatment of ADHD and Oppositional Symptoms

A. In situations where stimulants improve some but not all symptoms of ADHD, with residual oppositional symptoms, augmentation of a stimulant with a selective α2-adrenergic agonist such as guanfacine XR may provide an additional selective boost to the NE system at α2A receptors, and resolve more completely these residual oppositional behaviors.3,4

B. The stimulant increases the DA and NE, while the selective α2-adrenergic agonist boosts the NE concentration to therapeutic levels.

REFERENCES


