Neurotransmission of Cognition, Part 2
Selective NRIs Are Smart Drugs: Exploiting Regionally Selective Actions on Both Dopamine and Norepinephrine to Enhance Cognition

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Issue: *Selective norepinephrine reuptake inhibitors such as atomoxetine increase both dopamine and norepinephrine in frontal cortex and may thereby enhance cognitive functioning in attention-deficit/hyperactivity disorder.*

SMART NEUROTRANSMITTERS IN FRONTAL CORTEX

Recent scientific advances are beginning to clarify both the anatomical substrates and pharmacologic basis of cognition. Executive functions such as problem solving activate neurons in dorsolateral prefrontal cortex (PFC) and utilize numerous "smart" neurotransmitters, including dopamine, norepinephrine, histamine, acetylcholine, and perhaps others.[1–3] Malfunction of the circuits that release these neurotransmitters can hypothetically lead to problems with executive functioning in numerous disorders, including attention-deficit/hyperactivity disorder (ADHD) as well as schizophrenia, major depressive disorder, and various dementias.[1–4]

Not surprisingly, therapeutic approaches to disorders associated with executive dysfunction increasingly involve drugs that enhance smart neurotransmission in frontal cortex. Cholinergic activity can be enhanced throughout the cortex by cholinesterase inhibitors,[3] and histamine release can be activated in PFC by the novel wake-promoting agent modafinil.[2] Atypical antipsychotics can increase dopamine release in PFC.[3] Stimulants can release both dopamine and norepinephrine in many brain regions, including not only PFC, but also subcortical areas that control motor functions and reward.[4] A novel approach that targets both dopamine and norepinephrine release in frontal cortex but not in subcortical areas is atomoxetine, the newly approved selective inhibitor of norepinephrine reuptake.[4,5]

DOPAMINE REUPTAKE INHIBITION IS STIMULATING BUT NOT VERY SMART

Dopamine reuptake inhibition can occur only where there are dopamine transporters. Because the frontal cortex contains very few dopamine transporters, dopamine reuptake inhibition does not increase dopamine in frontal cortex.[4,6–8] Thus, dopamine diffuses over a much wider area than its own synapse and affects a much greater area of the frontal cortex, which may be linked to its hypothesized key regulatory role in cognitive function.[6–8] By contrast, inhibiting dopamine transporters in striatum and nucleus accumbens, areas that are rich in dopamine transporters, causes dopamine to increase in these areas.[4] Regional differences in the distribution of dopamine transporters can explain why dopamine reuptake inhibition leads to stimulation of motor activity and euphoria, but not cognitive improvement.

Stimulants such as methylphenidate and amphetamine are not only inhibitors of dopamine transporters, but also releasers of both dopamine and norepinephrine.[3,4] This ability of stimulants to release dopamine and norepinephrine in cortex is hypothetically responsible for their ability to improve cognitive functioning. On the other hand, the combination of dopamine transporter inhibition plus the

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Take-Home Points

- Enhancing dopamine and norepinephrine release in frontal cortex may be linked to the therapeutic efficacy of stimulants in attention-deficit/hyperactivity disorder.
- Since few dopamine transporters are present in frontal cortex, dopamine is inactivated there by norepinephrine transporters but not by dopamine transporters. A novel way to enhance dopamine in frontal cortex is thus to inhibit norepinephrine reuptake.
- Selective norepinephrine reuptake inhibitors such as atomoxetine are able to increase both dopamine and norepinephrine in the frontal cortex without increasing dopamine in subcortical areas. This should theoretically lead to cognitive enhancement without abuse liability.

release of dopamine in nucleus accumbens is hypothetically responsible for the psychotomimetic effects, euphoria, reinforcement, and abuse potential of stimulants. Moreover, such combined actions of stimulants in striatum may be responsible for both inducing hyperactive motor behaviors in normals and reducing hyperactive motor behaviors in patients with the hyperactive form of ADHD.

NOREPINEPHRINE REUPTAKE INHIBITION IS SMART

Recent investigations confirm that the selective norepinephrine reuptake inhibitor (NRI) atomoxetine, which inhibits the reuptake of norepinephrine without inhibiting the reuptake of dopamine, leads to robust increases in both dopamine and norepinephrine in PFC, without increasing dopamine in either nucleus accumbens or striatum.[4] Because dopamine hitchhikes on norepinephrine neurons, its area of distribution increases in PFC but not in accumbens or striatum, where there are relatively few noradrenergic nerve terminals.[6] This may explain why NRIs, unlike stimulants, are not psychotomimetic and do not have abuse potential. In fact, clinical studies with atomoxetine have demonstrated that selective norepinephrine reuptake inhibition leads to therapeutic actions for cognition in ADHD without psychotomimetic effects or abuse potential.[5]

Both dopamine and norepinephrine are affected when frontal cortex norepinephrine transporters are blocked by one of the many agents that have this property, either selectively (e.g., atomoxetine, reboxetine, desipramine) or nonselectively (e.g., venlafaxine, duloxetine, and many tricyclic antidepressants). These drugs all enhance the action dopamine and norepinephrine but only in frontal cortex, hypothetically leading to not only antidepressant actions but also cognitive enhancement.

EXPLOITING NOREPINEPHRINE REUPTAKE INHIBITION TO IMPROVE COGNITION

Since numerous disorders associated with cognitive dysfunction may be improved by enhancing the smart neurotransmitters dopamine and norepinephrine in dorsolateral PFC, there may be additional applications of NRIs beyond the treatment of inattentiveness in ADHD. Targeting patients who have problems with working memory secondary to any number of disorders—ranging from major depression to schizophrenia to various dementias for treatment with NRIs—may lead to expanded uses for this therapeutic strategy and also help clarify which cognitive disorders can benefit from more dopamine and norepinephrine in PFC. ◆

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