Neurotransmission of Cognition, Part 1
Dopamine Is a Hitchhiker in Frontal Cortex: Norepinephrine Transporters Regulate Dopamine

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Issue: *Since the frontal cortex has a low density of dopamine transporters, dopamine has to be inactivated there by hitching a ride on the norepinephrine transporter of neighboring norepinephrine neurons.*

PROMISCUOUS TRANSPORTERS

It is well known that the monoamine neurotransmitters norepinephrine, dopamine, and serotonin each have their own molecularly distinct presynaptic transporters, sometimes also called "reuptake pumps."[1,2] It is also common knowledge that most antidepressants block one or another of these transporters and that the pattern of selectivity of antidepressants results in their clinical effects (e.g., serotonin selective vs. norepinephrine selective vs. dual serotonin and norepinephrine actions).[2] What is less widely appreciated is the fact that the transporters themselves are promiscuous and not all that selective.[3,4] Thus, numerous drugs and neurotransmitters can be transported by these reuptake pumps (e.g., fenfluramine and "Ecstasy" [3,4-methylenedioxymethamphetamine; MDMA] by the serotonin transporter; norepinephrine and dopamine both by the norepinephrine transporter).[1–4]

This nonselectivity of the transporter comes into play only when something other than its own neurotransmitter shows up in the neighborhood. We used to think that this promiscuous selectivity happened only when certain drugs capable of interacting with the transporters were administered or when pathologic circumstances were present, but we are now learning that it happens normally in frontal cortex to enhance the geographic scope of dopamine neurotransmission there as well as dopamine's ability to regulate cognitive functioning.[1,3,4]

NEUROTRANSMISSION DIFFERS FOR SUBCORTICAL VERSUS CORTICAL DOPAMINE

Neurotransmission of dopamine in subcortical regions such as the basal ganglia and limbic areas (e.g., nucleus accumbens) is synaptic, because in these places, dopamine transporters are plentiful on dopaminergic axon terminals, thus limiting the diffusion of dopamine away from dopamine synapses.[3–5] Furthermore, relatively few noradrenergic nerve terminals are present in these same subcortical brain areas, so the norepinephrine transporter has little or no regulatory role for dopamine in these places.

On the other hand, dopamine neurotransmission in the frontal cortex is far different, because there are very few dopamine transporters present in frontal cortex.[3–5] This allows dopamine to diffuse away from the dopamine synapse after it is released, where it is free to affect any dopamine receptor it can reach. The process of distant, nonsynaptic neurotransmission is sometimes called "volume neurotransmission."[2] This ability of dopamine to navigate over wide areas of frontal cortex may be linked to its hypothesized key regulatory role in cognitive functions, such as working memory and attention.[2,5]

Dopamine inactivation in frontal cortex thus does not depend on dopamine reuptake; rather, it depends on diffusion, metabolism by the enzyme COMT (catechol-*O*-methyl transferase),[5] and reaching noradren-

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Take-Home Points

- Neurotransmission of dopamine in subcortical regions is synaptic, because dopamine transporters are plentiful on dopaminergic axon terminals there.
- By contrast, neurotransmission of dopamine in frontal cortex is both synaptic and nonsynaptic, because dopamine transporters are not plentiful there.
- Consequently, after being released from dopamine synapses in frontal cortex, dopamine diffuses away from the synapse to neighboring norepinephrine neurons, which inactivate dopamine by transporting it into their presynaptic terminals.

ergic nerve terminals that transport dopamine into the norepinephrine neurons.[1,3,4] The norepinephrine transporter, in fact, has even higher affinity for dopamine than it does for norepinephrine. This arrangement makes it possible for dopamine to diffuse over a much wider area than its own synapse, and thus affect a much greater area of frontal cortex than basal ganglia or nucleus accumbens, for example.

TWO FOR THE PRICE OF ONE

It is now clear that noradrenergic neurons play a key regulatory role over dopaminergic function in frontal cortex, and by extension, over dopamine's ability to regulate cognition. Not only does dopamine hitch a ride on the norepinephrine reuptake pump, it gets co-stored in synaptic vesicles with norepinephrine in noradrenergic neurons. Because of this, both dopamine and norepinephrine get released when frontal cortex noradrenergic nerves fire: 2 neurotransmitters for the price of 1 under physiologic conditions in this region of the brain.

TRANSPORTER-SELECTIVE DRUGS ARE NOT NECESSARILY TRANSMITTER SELECTIVE

These new discoveries on the regulation of frontal cortex dopamine by norepinephrine neurons will change how we use agents that act on neurotransmitter transporters. We now know that transporter-selective reuptake inhibitors are not necessarily transmitter-selective reuptake inhibitors.[3] How does this translate into practical psychopharmacology? For example, if we want to increase dopamine in frontal cortex therapeutically, we won't give a selective dopamine reuptake inhibitor because there are no dopamine transporters there. We can give a dopamine-releasing stimulant, but this would also enhance dopamine release in subcortical areas, which may not be desired. Or, we can give something that blocks the norepinephrine reuptake pump and increase both dopamine and norepinephrine in cortex, but only norepinephrine in subcortical areas, which may be a more favorable portfolio of actions when treating cognitive symptoms.[4]

In summary, new insights into the regulation of dopamine and norepinephrine in frontal cortex demonstrate that the transporter for dopamine does not regulate dopamine activity, but the transporter for norepinephrine does. Exploiting these actions with currently available drugs can lead to enhancing dopamine, norepinephrine, or both in frontal cortex, which could have therapeutic actions on cognition in a variety of disorders including depression, schizophrenia, and attention-deficit/hyperactivity disorder.[4] ◆

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