

Neurotransmission of Cognition, Part 3

Mechanism of Action of Selective NRIs: Both Dopamine and Norepinephrine Increase in Prefrontal Cortex

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Issue: *Selective norepinephrine reuptake inhibitors exploit the fact that dopamine transporters are absent in prefrontal cortex, so dopamine has to hitchhike a ride on the norepinephrine transporter in order to be inactivated. Thus, blocking norepinephrine transporters leads to an increase in both dopamine and norepinephrine levels in prefrontal cortex as well as improvement in cognition in attention-deficit/hyperactivity disorder.*

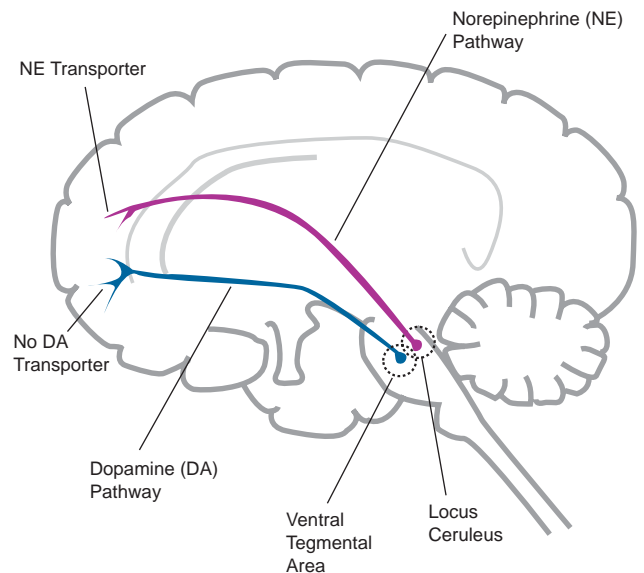
New discoveries about how dopamine and norepinephrine are regulated in the prefrontal cortex (PFC) run counter to classical pharmacologic expectations of how these neurotransmitters act in the rest of the brain.¹⁻⁶ In the PFC, dopamine reuptake inhibitors do not increase dopamine, but norepinephrine reuptake inhibitors (NRIs) do. The nature of counterintuitive findings like these can be initially confusing, but when understood, they are striking and can lead to a paradigm shift in the way in which psychopharmacology is applied to develop novel treatments. Just such a situation is the case for the new selective NRI atomoxetine. As a selective NRI, it increases norepinephrine as expected, but is now known to increase dopamine as well in PFC, possibly contributing to its recently demonstrated actions in improving cognition in attention-deficit/hyperactivity disorder.^{7,8} Here we illustrate this newly clarified regulation of dopamine in PFC and show how a norepinephrine reuptake inhibitor increases both dopamine and norepinephrine activity in prefrontal cortex.

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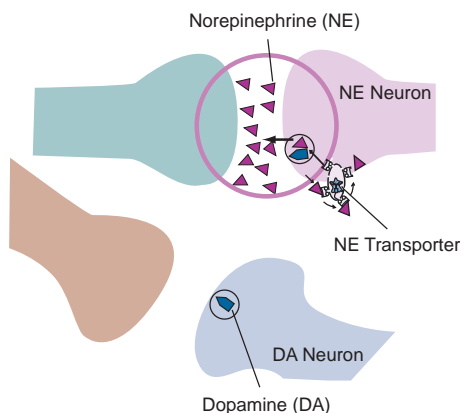
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Figure 1. Projections of Noradrenergic and Dopaminergic Pathways to Prefrontal Cortex



Dopamine projections in the mesocortical pathway arise from neurons in the ventral tegmental area of the brainstem. Norepinephrine projections arise from neurons in the locus ceruleus. Note that norepinephrine transporters are present on presynaptic norepinephrine axon terminals, but no dopamine transporters are present on presynaptic dopamine axon terminals.

Figure 2. Normal Norepinephrine Release



Norepinephrine release in prefrontal cortex is synaptic, and its actions are rapidly terminated by norepinephrine transporters prior to widespread diffusion away from the synapse, which is the classical pattern of neurotransmitter regulation in monoamine synapses.

Figure 3. Normal Dopamine (DA) Release

Dopamine in prefrontal cortex normally diffuses beyond the dopamine synapse after its release, because no dopamine transporters are present on presynaptic dopamine nerve terminals here, leading to a much wider distribution of dopamine than is normally allowed by synapses containing presynaptic monoamine transporters (see Figure 2). In fact, dopamine is free to diffuse to distant norepinephrine (NE) synapses where the norepinephrine transporter actually pumps dopamine into its neurons to terminate dopamine action. The ability of dopamine to navigate far from its synapses allows it to affect any dopamine receptor it can reach within its diffusion radius, perhaps contributing to dopamine's important role in cognition.

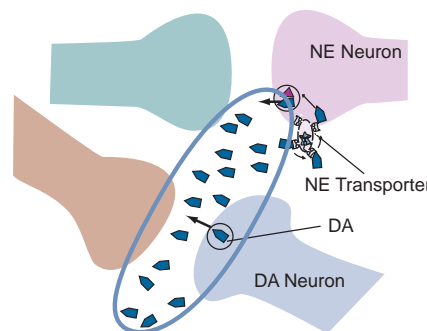
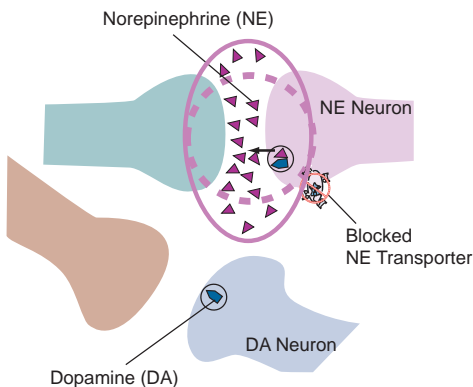


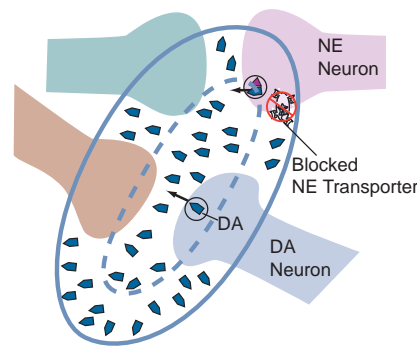
Figure 4. Effects on Norepinephrine Release When Norepinephrine Transporters in Prefrontal Cortex Are Inhibited



Norepinephrine is now free to build up and diffuse further away from the synapse. The normal diffusion radius of norepinephrine is shown as a dotted-line circle (see also Figure 2). Note that this area is expanded after blockade of norepinephrine transporters, as indicated by the larger, solid-line oval.

Figure 5. Effects on Dopamine (DA) Release When Norepinephrine (NE) Transporters in Prefrontal Cortex Are Inhibited

When dopamine is no longer inactivated by the norepinephrine transporter, dopamine diffuses extensively within prefrontal cortex, which may explain why norepinephrine reuptake inhibitors can have profound cognitive actions, since they enhance not only norepinephrine actions as shown in Figure 4, but also dopamine actions in prefrontal cortex as shown here. These actions may be helpful not only in attention-deficit/hyperactivity disorder, but possibly in other disorders that can be associated with cognitive dysfunction, from depression to dementia to schizophrenia. The normal diffusion radius of dopamine is shown as a dotted-line oval (see also Figure 3). Note that this area is expanded after blockade of norepinephrine transporters, as indicated by the larger, solid-line oval.



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