Nitric Oxide Physiology and Pharmacology

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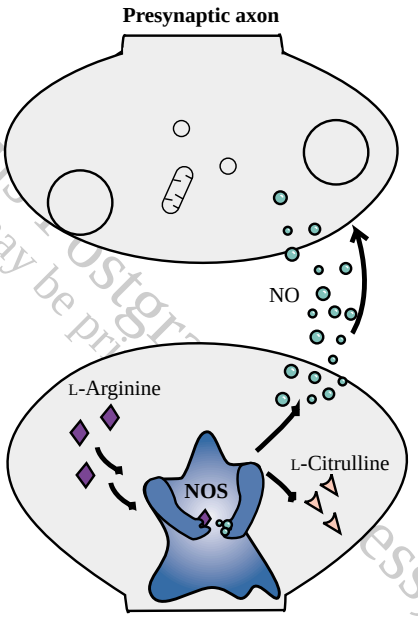
Issue: *Nitric oxide gas (NO) is an unconventional neurotransmitter that is synthesized upon demand. In the brain, it may allow postsynaptic elements to talk back to presynaptic neurons. In peripheral tissues it mediates smooth muscle relaxation. Various pharmacologic agents can enhance or reduce the actions of NO.*

Take-Home Points

- Certain cells possess the enzyme nitric oxide synthase (NOS), which forms NO from the amino acid arginine
- NO is synthesized upon demand and then diffuses to receptor sites within the enzyme guanylyl cyclase to cause this enzyme to synthesize cyclic GMP
- cGMP mediates physiologic changes in the cells where it is formed. For example, in the penis it relaxes smooth muscle and produces a physiologic erection
- The pharmacology of NO includes drugs that can reduce nitric oxide synthesis (serotonin selective reuptake inhibitors), enhance nitric oxide synthesis (dopamine agonists such as apomorphine), and reduce cGMP destruction (sildenafil)

Figure 1



During neurotransmission in the brain, some postsynaptic elements form nitric oxide gas (NO) in response to nerve stimulation. The enzyme nitric oxide synthase (NOS) synthesizes NO[1–4] by converting the amino acid arginine into both NO and the by-product citrulline. This free NO is then able to diffuse ("talk back") to the presynaptic neuron, which could be how 2-way communication between presynaptic and postsynaptic elements occurs in some CNS synapses.

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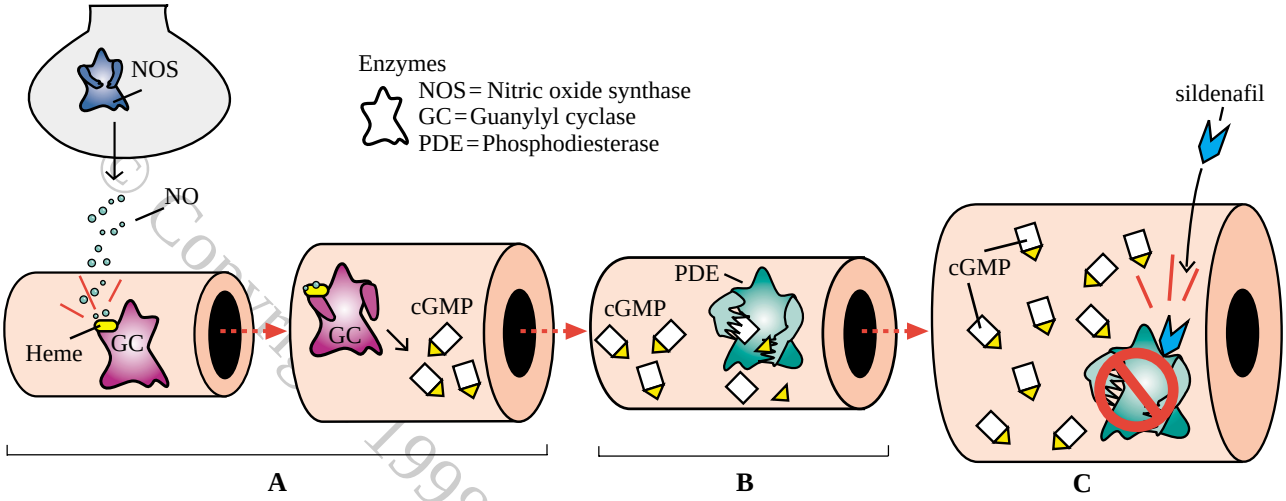
Figure 2



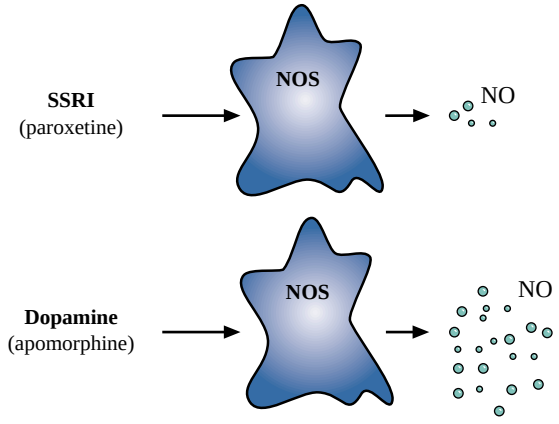
A. The free NO, which has been synthesized upon demand, diffuses to receptor sites within the enzyme quanylyl cyclase (GC) and causes it to convert GTP to cyclic GMP.[1–4] In the example presented here, NO is synthesized in a presynaptic neuron and diffuses to its receptors in GC within postsynaptic smooth muscle. The NO receptor is actually iron in the enzyme GC. NO binding causes the iron-containing heme group to change its 3-dimensional shape and thereby increase the production of cGMP from GTP.

B. cGMP mediates physiologic changes in the cells where it is formed.[1–4] For example, in the penis it relaxes smooth muscle and produces a physiologic erection. cGMP is normally destroyed by the enzyme phosphodiesterase (PDE), of which there are several different subtypes.[5–8] In the penis, once PDE removes sufficient cGMP, the penis detumesces.[5,6]

C. Erectile disturbances may not allow sufficient cGMP to be formed for an adequate erection to occur. Thus, it has been proposed that if cGMP could somehow be enhanced, perhaps so could physiologic erections. In fact, enhancement occurs with the novel phosphodiesterase inhibitor sildenafil (Viagra), about to be released by the FDA.[7,8] It just so happens that phosphodiesterase in the penis is a specific subtype that is not present in all tissues, and targeting it leads to tissue selective phosphodiesterase inhibition. The value of this specificity is better systemic tolerability even when sildenafil is taken orally. The resulting increase of cGMP during sexual arousal enhances physiologic erections—a much more spontaneous and natural response than mechanical manipulations for most men.

Clinical trials show that sexual arousal previously insufficient to cause an erection may now do so; arteries too clogged with cholesterol from atherosclerosis, smoking, or diabetes to create a robust erection may now enable an erection; nerves too sick from diabetes or surgery (or even poorly fitting bicycle seats) may now work well enough so that an erection can occur.[5,7,8]

Figure 3



The pharmacology of NO includes drugs that can reduce nitric oxide synthesis (serotonin selective reuptake inhibitors; SSRIs)[9] as well as enhance nitric oxide synthesis (dopamine agonists such as apomorphine). Perhaps this relationship explains, in part, the sexual dysfunction associated with SSRIs as well as the ability of dopamine agonists to mitigate it.[10]

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