Brain Fumes: Yes, We Have NO Brain Gas

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Issue: *Nitric oxide (NO) is improbable as a conventional neurotransmitter. It is not an amine, amino acid, or peptide; it is not stored in synaptic vesicles or released by exocytosis; and it does not interact with specific receptor subtypes in neuronal membranes. However, NO is synthesized upon demand in the brain, diffuses to receptor sites within the enzyme guanylyl cyclase, and has neurotransmitter-like functions.*

Take-Home Points

- A diffusible gas, nitric oxide (NO) is synthesized in the CNS where it acts as a novel neuronal messenger
- NO may play a role in synaptic plasticity and in memory formation
- NO may also be involved in excitotoxicity and neurodegeneration

No Laughing Matter

Nitrous oxide (N_2O) is "laughing gas," one of the earliest known inhalation anesthetics. Nitric oxide (NO) is a far different gas, although the two are often confused. It is NO that is made by the brain and used as a neurotransmitter, not N_2O.[1,2] Incredible as it may appear, NO, a poisonous unstable gas, which is part of car fumes and helps deplete the ozone layer, is also a chemical messenger both in the brain and in blood vessels.

Yes, NO Synthesis by Neurons

Certain neurons possess the enzyme nitric oxide synthase (NOS), which forms NO from the amino acid arginine (see Figure). In moderate amounts, NO diffuses to adjacent neurons and provokes the formation of the second messenger cyclic guanosine monophosphate (cGMP) by activating the enzyme guanylyl cyclase. NO is not made in advance nor is it stored but seems to be made on demand and released by simple diffusion. Glutamate and calcium can trigger the formation of NO by activating NOS.[1,2]

No NO Receptors

In striking contrast to classical neurotransmitters, which have numerous types and subtypes of membrane receptors on neurons, there are no NO membrane receptors.[1,2] Rather, the receptor target of NO is iron in the active site of guanylyl cyclase. Once NO binds to the iron, guanylyl cyclase is activated, and cGMP is formed. Interestingly, another component of automobile exhaust, carbon monoxide (CO), also appears to be formed by the brain and, along with NO, appears to be a key regulator of cGMP in the brain.[2]

Yes, NO Neurotransmitter Function

The first known messenger functions for NO were described in blood vessels.[1,3] By relaxing blood vessels, NO can regulate penile erections and mediate the ability of nitroglycerin to treat cardiac angina. NO also appears to be a key regulator of blood pressure, platelet aggregation, and peristalsis.[1,2]

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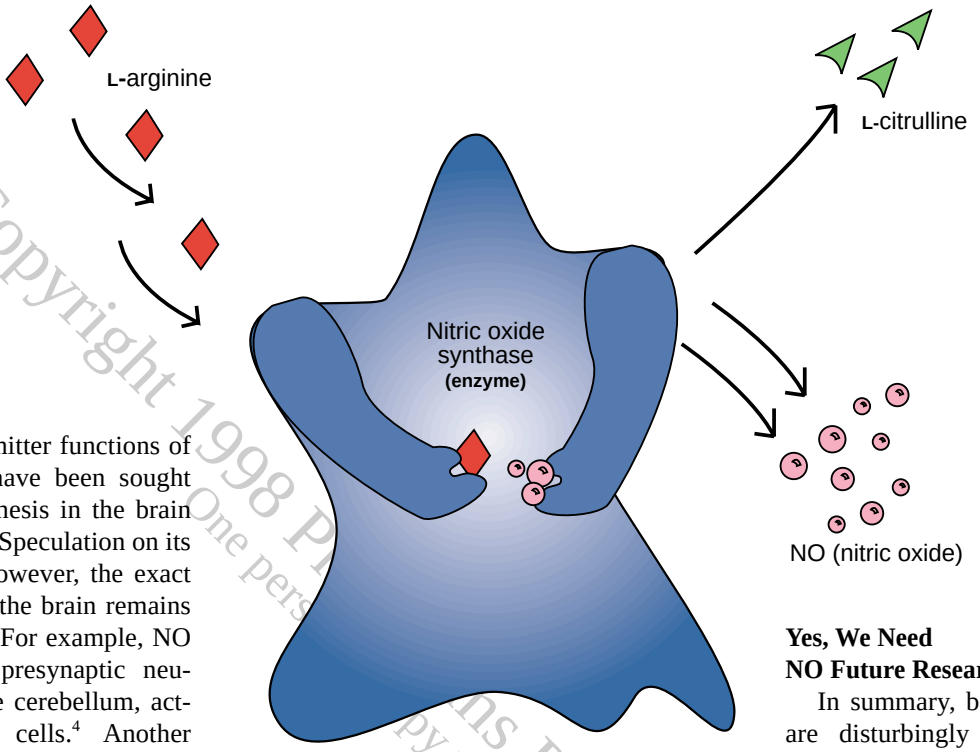

The neurotransmitter functions of NO in the CNS have been sought ever since its synthesis in the brain was demonstrated. Speculation on its functions exists; however, the exact function of NO in the brain remains somewhat elusive. For example, NO appears to be a presynaptic neurotransmitter in the cerebellum, acting on Purkinje cells.[4] Another proposal is that NO is the long sought-after "retrograde neurotransmitter."[4] Since presynaptic neurotransmitters have long been known to activate postsynaptic receptors, it seems logical that communication in this direction should be accompanied by some form of back-talk from the postsynaptic site to the presynaptic neuron. The idea is that NO is formed postsynaptically in some synapses when postsynaptic activation is prompted by a presynaptic neurotransmitter. It then diffuses back to the presynaptic neuron, carrying information in reverse.

Some specific functions carried by this NO message may be to induce the neuronal signals responsible for memory formation, namely, LTP (long-term potentiation) and LTD (long-term depression).[4] NO may use these same neuronal signals to mediate neuronal plasticity, a process by which certain synapses gain a new function.

Yes, NO Neurotoxicity

We have long known that NO is responsible for the tumoricidal and bactericidal actions of macrophages.[1–3,5]; that is, the killing potential of macrophages is activated when they form NO. Large amounts of NO can "nuke" bacteria and tumor cells when the free radicals generated by NO rip them apart.

In neurons, a bit of NO leads to neuronal communication when guanylyl cyclase is activated to form the second messenger cGMP. However, when a lot of NO is formed in neurons, it can tear apart neurons just like it does bacteria and tumor cells. Excessive NO is hypothetically formed during ischemia and stroke, leading to lethal levels and neuronal destruction.[6] New therapeutics aimed at preventing excess NO formation may prove to be effective treatments for stroke.[1–4]

Yes, We Need NO Future Research

In summary, brain fumes are disturbingly like auto emissions, containing both nitric oxide and carbon monoxide. Together, these brain gases are key regulators of cGMP, which in turn may control retrograde messages, memory, and synaptic plasticity. Overdosing on brain fumes may be lethal to neurons. NO research may be key to future neuroscience understanding.

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