Nitrous oxide

For Other uses, see NOS.

Nitrous oxide		
[[Image:Nitrous-oxide-3D-vdW.png		Nitrous oxide – space-filling model]]
[[Image:Nitrous-oxide-dimensions-3D-balls.png		Nitrous oxide's bond lengths]]
[[Image:Nitrous-oxide-2D-VB.svg		Nitrous oxide's canonical forms]]
Identifiers		
CAS number	10024-97-2 [1] ✓	
PubChem	948 [2]	
ChemSpider	923 [3] ✓	
UNII	K50XQU1029 [4] ✓	
UN number	1070 (compressed) 2201 (liquid)	
KEGG	D00102 [5] ✓	
ChEBI	CHEBI:17045 [6] ✓	
RTECS number	QX1350000	
ATC code	N01 AX13 [7]	
Jmol-3D images	Image 1 [8]	
Properties		
Molecular formula	N_2O	
Molar mass	44.013 g/mol	
Appearance	colorless gas	
Density	1.977 g/L (gas)	
Melting point	−90.86 °C (182.29 K)	
Boiling point	−88.48 °C (184.67 K)	
Solubility in water	0.15 g/100 ml (15 °C)	
Solubility	soluble in alcohol, ether, sulfuric acid	
log P	0.35	
Vapor pressure	5150 kPa (20 °C)	
Refractive index (n_D)	1.330	
Structure		
Molecular shape	linear, $C_{\infty v}$	
Dipole moment	0.166 D	
Thermochemistry		

Std enthalpy of formation $\Delta_f H^{o}_{298}$	+82.05 kJ/mol	
Standard molar entropy S^{o}_{298}	219.96 J K^{-1} mol^{-1}	
Pharmacology		
Routes of administration	Inhalation	
Metabolism	0.004%	
Elimination half-life	5 minutes	
Excretion	Respiratory	
Pregnancy category	C(US)	
Hazards		
MSDS	Ilo.org [9], ICSC 0067	
EU Index	Oxidant [**O**]	
NFPA 704		
Flash point	Non-flammable	
Related compounds		
Related nitrogen oxides	Nitric oxide Dinitrogen trioxide Nitrogen dioxide Dinitrogen tetroxide Dinitrogen pentoxide	
Related compounds	Ammonium nitrate Azide	
✓ (what is this?) (verify) [10] Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)		
Infobox references		

Nitrous oxide, commonly known as **laughing gas** or **sweet air**,[11] is a chemical compound with the formula N_2O. It is an oxide of nitrogen. At room temperature, it is a colorless non-flammable gas, with a slightly sweet odor and taste. It is used in surgery and dentistry for its anesthetic and analgesic effects. It is known as "laughing gas" due to the euphoric effects of inhaling it, a property that has led to its recreational use as a dissociative anesthetic. It is also used as an oxidizer in rocketry and in motor racing to increase the power output of engines. At elevated temperatures, nitrous oxide is a powerful oxidizer similar to molecular oxygen.

Nitrous oxide gives rise to NO (nitric oxide) on reaction with oxygen atoms, and this NO in turn reacts with ozone. As a result, it is the main naturally occurring regulator of stratospheric ozone.

History

The gas was first synthesized by English natural philosopher and chemist Joseph Priestley in 1772, who called it *phlogisticated nitrous air* (see phlogiston).[12] Priestley published his discovery in the book *Experiments and Observations on Different Kinds of Air (1775)*, where he described how to produce the preparation of "nitrous air diminished", by heating iron filings dampened with nitric acid.[13]

Early use (1794–1843)

The first important use of nitrous oxide was made possible by Thomas Beddoes and James Watt, who worked together to publish the book *Considerations on the Medical Use and on the Production of Factitious Airs (1794)*. This book was important for two reasons. First, James Watt had invented a novel machine to produce "Factitious Airs" (i.e. nitrous oxide) and a novel "breathing apparatus" to inhale the gas. Second, the book also presented the new medical theories by Thomas Beddoes, that tuberculosis and other lung diseases could be treated by inhalation of "Factitious Airs".[14]

The machine to produce "Factitious Airs" had three parts: A furnace to burn the needed material, a vessel with water where the produced gas passed through in a spiral pipe (for impurities to be "washed off"), and finally the gas cylinder with a gasometer where the gas produced, 'air,' could be tapped into portable air bags (made of airtight oily silk). The breathing apparatus consisted of one of the portable air bags connected with a tube to a mouthpiece. With this new equipment being engineered and produced by 1794, the way was paved for clinical trials, which began when Thomas Beddoes in 1798 established the *"Pneumatic Institution for Relieving Diseases by Medical Airs"* in Clifton (Bristol). In the basement of the building, a large scale machine was producing the gases under the supervision of a young Humphry Davy, who was encouraged to experiment with new gases for patients to inhale.[14] The first important work of Davy was examination of the nitrous oxide, and the publication of his results in the book: *Researches, Chemical and Philosophical (1800)*. In that publication, Davy notes the analgesic effect of nitrous oxide at page 465 and its potential to be used for surgical operations at page 556.[15]

Despite Davy's discovery that inhalation of nitrous oxide could relieve a conscious person from pain, another 44 years elapsed before doctors attempted to use it for anaesthesia. The use of nitrous oxide as a recreational drug at "laughing gas parties", primarily arranged for the British upper class, became an immediate success beginning in 1799. While the effects of the gas generally make the user feel stuporous, dreamy and sedated, some people also "get the giggles" in a state of euphoria, and frequently, erupt in laughter.[16]

Anesthetic use

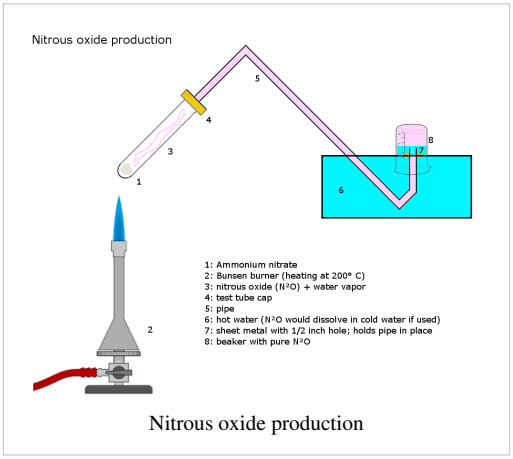
Further information: Nitrous oxide and oxygen

The first time nitrous oxide was used as an anesthetic drug in the treatment of a patient was when dentist Horace Wells, with assistance by Gardner Quincy Colton and John Mankey Riggs, demonstrated insensitivity to pain from a dental extraction on 11 December 1844.[17] In the following weeks, Wells treated the first 12–15 patients with nitrous oxide in Hartford, and according to his own record only failed in two cases.[18] In spite of these convincing results being reported by Wells to the medical society in Boston already in December 1844, this new method was not immediately adopted by other dentists. The reason for this was most likely that Wells, in January 1845 at his first public demonstration towards the medical faculty in Boston, had been partly unsuccessful, leaving his colleagues doubtful regarding its efficacy and safety.[19] The method did not come into general use until 1863, when Gardner Quincy Colton successfully started to use it in all his "Colton Dental Association" clinics, that he had just established in New Haven and New York City.[14] Over the following three years, Colton and his associates successfully administered nitrous oxide to more than 25,000 patients.[20] Today, nitrous oxide is used in dentistry as an anxiolytic, as an adjunct to local anesthetic. While nitrous oxide does have some anesthetic properties, especially with regards to soft tissues like the gums, it is not suitable for suppressing the pain caused by dental work.

In hospitals, nitrous oxide was however found not to be a strong enough anesthetic for the use in large operations. Being a stronger and more potent anesthetic, sulfuric ether was instead demonstrated and accepted for use in October 1846, along with chloroform in 1847.[14] When Joseph Thomas Clover invented the "gas-ether inhaler" in 1876, it however became a common practice at hospitals to initiate all anesthetic treatments with a mild flow of nitrous oxide, and then gradually increase the anaesthesia with the stronger ether/chloroform. Clover's gas-ether inhaler was designed to supply the patient with nitrous oxide and ether at the same time, with the exact mixture being controlled by the operator of the device. It remained in use by many hospitals until the 1930s.[20] Although hospitals today are using a more advanced anaesthetic machine, these machines still use the same principle launched with Clover's gas-ether inhaler: To initiate the anesthesia with nitrous oxide, before the administration of a more powerful anesthetic.

Production

Nitrous oxide is most commonly prepared by careful heating of ammonium nitrate, which decomposes into nitrous oxide and water vapor.[21] The addition of various phosphates favors formation of a purer gas at slightly lower temperatures. One of the earliest commercial producers was George Poe in Trenton, New Jersey.[22]



Nitrous oxide production

$$NH_4NO_3\,(s) \rightarrow 2\,H_2O\,(g) + N_2O\,(g)$$

This reaction occurs between 170 and 240 °C, temperatures where ammonium nitrate is a moderately sensitive explosive and a very powerful oxidizer. Above 240 °C the exothermic reaction may accelerate to the point of detonation, so the mixture must be cooled to avoid such a disaster. Superheated steam is used to reach reaction temperature in some turnkey production plants.[23]

Downstream, the hot, corrosive mixture of gases must be cooled to condense the steam, and filtered to remove higher oxides of nitrogen. Ammonium nitrate smoke, as an extremely persistent colloid, will also have to be removed. The cleanup is often done in a train of 3 gas washes; namely base, acid and base again. Any significant amounts of nitric oxide (NO) may not necessarily be absorbed directly by the base (sodium hydroxide) washes.

The nitric oxide impurity is sometimes chelated out with ferrous sulfate, reduced with iron metal, or oxidised and absorbed in base as a higher oxide. The first base wash may (or may not) react out much of the ammonium nitrate smoke. However, this reaction generates ammonia gas, which may have to be absorbed in the acid wash.

Other routes

The direct oxidation of ammonia may someday rival the ammonium nitrate pyrolysis synthesis of nitrous oxide mentioned above. This capital-intensive process, which originates in Japan, uses a manganese dioxide-bismuth oxide catalyst:[24]

$$2\,NH_3 + 2\,O_2 \rightarrow N_2O + 3\,H_2O$$

Higher oxides of nitrogen are formed as impurities. In comparison, uncatalyzed ammonia oxidation (i.e. combustion or explosion) goes primarily to N_2 and H_2O.

Nitrous oxide can be made by heating a solution of sulfamic acid and nitric acid. Many gases are made this way in Bulgaria.[25]

$$HNO_3 + NH_2SO_3H \rightarrow N_2O + H_2SO_4 + H_2O$$

There is no explosive hazard in this reaction if the mixing rate is controlled. However, as usual, toxic higher oxides of nitrogen are formed.

Nitrous oxide is produced in large volumes as a by-product in the synthesis of adipic acid; one of the two reactants used in nylon manufacture.[26] [27] This might become a major commercial source, but will require the removal of higher oxides of nitrogen and organic impurities. Currently much of the gas is decomposed before release for environmental protection. Greener processes may prevail that substitute hydrogen peroxide for nitric acid oxidation; hence no generation of oxide of nitrogen by-products.

Hydroxylammonium chloride can react with sodium nitrite to produce N_2O as well:

$$NH_3OH^+Cl^- + NaNO_2 \rightarrow N_2O + NaCl + 2\ H_2O$$

If the nitrite is added to the hydroxylamine solution, the only remaining byproduct is salt water. However, if the hydroxylamine solution is added to the nitrite solution (nitrite is in excess), then toxic higher oxides of nitrogen are also formed. Also, HNO_3 can be reduced to N_2O by $SnCl_2$ and HCl mixture:

$$2\ HNO_3 + 8\ HCl + 4\ SnCl_2 \rightarrow 5\ H_2O + 4\ SnCl_4 + N_2O$$

Natural production of N_2O occurs through the process of denitrification in oxygen-poor soils and marine environments, in which denitrifying bacteria respire NO_3^-.

Applications

Rocket motors

Nitrous oxide can be used as an oxidizer in a rocket motor. This has the advantages over other oxidizers in that it is non-toxic and, due to its stability at room temperature, easy to store and relatively safe to carry on a flight. As a secondary benefit it can be readily decomposed to form breathing air. Its high density and low storage pressure enable it to be highly competitive with stored high-pressure gas systems.

In a 1914 patent, American rocket pioneer Robert Goddard suggested nitrous oxide and gasoline as possible propellants for a liquid-fueled rocket. Nitrous oxide has been the oxidizer of choice in several hybrid rocket designs (using solid fuel with a liquid or gaseous oxidizer). The combination of nitrous oxide with hydroxyl-terminated polybutadiene fuel has been used by SpaceShipOne and others. It is also notably used in amateur and high power rocketry with various plastics as the fuel.

Nitrous oxide can also be used in a monopropellant rocket. In the presence of a heated catalyst, N_2O will decompose exothermically into nitrogen and oxygen, at a temperature of approximately 1300 °C. Because of the large heat release, the catalytic action rapidly becomes secondary as thermal autodecomposition becomes dominant. In a vacuum thruster, this can provide a monopropellant specific impulse (I_{sp}) of as much as 180 s. While noticeably less than the I_{sp} available from hydrazine thrusters (monopropellant or bipropellant with nitrogen tetroxide), the decreased toxicity makes nitrous oxide an option worth investigating.

Specific impulse (I_{sp}) can be improved by blending a hydrocarbon fuel with the nitrous oxide inside the same storage tank, becoming a nitrous oxide fuel blend (NOFB) monopropellant. This storage mixture does not incur the danger of spontaneous ignition, since N_2O is chemically stable. When the nitrous oxide decomposes by a heated catalyst, high temperature oxygen is released and rapidly ignites the hydrocarbon fuel-blend. NOFB monopropellants are capable of I_{sp} greater than 300 seconds, while avoiding the toxicity associated with hypergolic propulsion systems.[28] [29] The low freezing point of NOFB eases thermal management compared to hydrazine and dinitrogen tetroxide—a valuable property for space storable propellants.

Nitrous oxide can also be used as a monopropellant, for example for use in rockets. For this, the nitrous oxide needs to be brought to a high enough temperature or a high enough pressure. Nitrous oxide is said to deflagrate somewhere around 600° Fahrenheit (315°Celsius). It can also easily be ignited using a combination of the two. At 600 psi for example, the required ignition energy is only 6 J, whereas N2O at 130 psi would not react even with a 2500 J

ignition energy input.[30] [31] [32] [33]

Internal combustion engine

In vehicle racing, nitrous oxide (often referred to as just "nitrous") allows the engine to burn more fuel and air, resulting in a more powerful combustion. The gas itself is not flammable at a low pressure/temperature, but it delivers more oxygen than atmospheric air by breaking down at elevated temperatures. Therefore, it is often mixed with another fuel that is easier to deflagrate.

Nitrous oxide is stored as a compressed liquid; the evaporation and expansion of liquid nitrous oxide in the intake manifold causes a large drop in intake charge temperature, resulting in a denser charge, further allowing more air/fuel mixture to enter the cylinder. Nitrous oxide is sometimes injected into (or prior to) the intake manifold, whereas other systems directly inject right before the cylinder (direct port injection) to increase power.

The technique was used during World War II by *Luftwaffe* aircraft with the GM-1 system to boost the power output of aircraft engines. Originally meant to provide the *Luftwaffe* standard aircraft with superior high-altitude performance, technological considerations limited its use to extremely high altitudes. Accordingly, it was only used by specialized planes like high-altitude reconnaissance aircraft, high-speed bombers, and high-altitude interceptor aircraft.

One of the major problems of using nitrous oxide in a reciprocating engine is that it can produce enough power to damage or destroy the engine. Very large power increases are possible, and if the mechanical structure of the engine is not properly reinforced, the engine may be severely damaged or destroyed during this kind of operation. It is very important with nitrous oxide augmentation of internal combustion engines to maintain proper operating temperatures and fuel levels to prevent "preignition", or "detonation" (sometimes referred to as "knocking" or "pinging"). Most problems that are associated with nitrous do not come from mechanical failure due to the power increases. Since nitrous allows a much denser charge into the cylinder it dramatically increases cylinder pressures. The increased pressure and temperature can cause problems such as melting the piston or valves. It may also crack or warp the piston or head and cause preignition due to uneven heating.

Automotive-grade liquid nitrous oxide differs slightly from medical-grade nitrous oxide. A small amount of sulfur dioxide is added to prevent substance abuse.[34]

Aerosol propellant

The gas is approved for use as a food additive (also known as E942), specifically as an aerosol spray propellant. Its most common uses in this context are in aerosol whipped cream canisters, cooking sprays, and as an inert gas used to displace oxygen, to inhibit bacterial growth, when filling packages of potato chips and other similar snack foods.

The gas is extremely soluble in fatty compounds. In aerosol whipped cream, it is dissolved in the fatty cream until it leaves the can, when it becomes gaseous and thus creates foam. Used in this way, it produces whipped cream four times the volume of the liquid, whereas whipping air into cream only produces twice the volume. If air were used as a propellant, oxygen would accelerate rancidification of the butterfat; nitrous oxide inhibits such degradation. Carbon dioxide cannot be used for whipped cream because it is acidic in water, which would curdle the cream and give it a seltzer-like 'sparkling' sensation.

However, the whipped cream produced with nitrous oxide is unstable and will return to a more or less liquid state within half an hour to one hour. Thus, the method is not suitable for decorating food that will not be immediately served.

Similarly, cooking spray, which is made from various types of oils combined with lecithin (an emulsifier), may use nitrous oxide as a propellant; other propellants used in cooking spray include food-grade alcohol and propane.

Users of nitrous oxide often obtain it from whipped cream dispensers that use nitrous oxide as a propellant (see above section), for recreational use as a euphoria-inducing inhalant drug. It is not harmful in small doses, but risks

due to lack of oxygen do exist (see *Recreational use below).*

In medicine

Further information: Nitrous oxide and oxygen

Medical grade N_2O tanks used in dentistry.

Nitrous oxide has been used for anesthesia in dentistry since December 1844, where Horace Wells made the first 12–15 dental operations with the gas in Hartford. Its debut as a generally accepted method however came in 1863, when Gardner Quincy Colton introduced it more broadly at all the Colton Dental Association clinics, that he founded in New Haven and New York city.[14] The first devices used in dentistry to administer the gas, known as Nitrous Oxide inhalers, were designed in a very simple way with the gas stored and breathed through a breathing bag made of rubber cloth, without a scavenger system and flowmeter, and with no addition of oxygen/air.[20] Today these simple and somewhat unreliable inhalers, of course have been replaced by the more modern relative analgesia machine, which is an automated machine designed to deliver a precisely dosed and breath-actuated flow of nitrous oxide mixed with oxygen, for the patient to inhale safely. The machine used in dentistry is designed as a more simplified version of the larger anaesthetic machine used by hospitals, as it doesn't feature the additional anaesthetic vaporiser and medical ventilator. The purpose of the machine allows for a simpler design, as it only delivers a mixture of nitrous oxide and oxygen for the patient to inhale, in order to depress the feeling of pain -while keeping the patient in a conscious state.

The relative analgesia machine typically feature a constant-supply flowmeter, which allow the proportion of nitrous oxide and the combined gas flow rate to be individually adjusted. The gas is administered by dentists through a demand-valve inhaler over the nose, which will only release gas when the patient inhales through the nose. Because nitrous oxide is minimally metabolized in humans (with a rate of 0.004%), it retains its potency when exhaled into the room by the patient, and can pose an intoxicating and prolonged exposure hazard to the clinic staff if the room is poorly ventilated. Where nitrous oxide is administered, a continuous-flow fresh-air ventilation system or nitrous scavenger system is used to prevent a waste-gas buildup.

Hospitals are administering nitrous oxide as one of the anesthetic drugs delivered by anaesthetic machines. Nitrous oxide is a weak general anesthetic, and so is generally not used alone in general anesthesia. In general anesthesia it is used as a carrier gas in a 2:1 ratio with oxygen for more powerful general anesthetic drugs such as sevoflurane or desflurane. It has a minimum alveolar concentration of 105% and a blood:gas partition coefficient of 0.46.

When nitrous oxide is inhaled as the only anesthetic drug, it is normally administered as a mixture with 30% gas and 70% oxygen.[35] The medical grade gas tanks, with the tradename Entonox and Nitronox contain a mixture with 50%, but this will normally be diluted to a lower percentage upon the operational delivery to the patient. Inhalation of nitrous oxide is frequently used to relieve pain associated with childbirth, trauma, oral surgery, and acute coronary syndrome (includes heart attacks). Its use during labor has been shown to be a safe and effective aid for women wanting to give birth without an epidural.[36] Its use for acute coronary syndrome is of unknown benefit.[37]

In Britain and British Columbia, Canada, Entonox and Nitronox are commonly used by ambulance crews (including unregistered practitioners) as a rapid and highly effective analgesic gas.

Nitrous oxide has been shown to be effective in treating a number of addictions including alcohol withdrawal.[38] [39]

Recreational use

Nitrous oxide can cause analgesia, depersonalization, derealization, dizziness, euphoria, and some sound distortion.[40] Research has also found that it increases suggestibility and imagination.[41] Inhalation of nitrous oxide for recreational use, with the purpose to cause euphoria and slight hallucinations, began as a phenomenon for the British upper class in 1799, known as "laughing gas parties". Until at least 1863, a low availability of equipment to produce the gas, combined with a low usage of the gas for medical purposes, meant it was a relatively rare phenomenon that mainly happened among students at medical universities. When equipment became more widely available for dentistry and hospitals, most countries also restricted the legal access to buy pure nitrous oxide gas cylinders to those sectors. As only medical staff and dentists today are legally allowed to buy the pure gas, the recreational use is also believed to be somewhat limited. The consumers union report from 1972, however found that the use of the gas for recreational purpose still take place in present time, based upon reports of its use in Maryland 1971, Vancouver 1972, and a survey made by Dr.Edward J.Lynn of its nonmedical use in Michigan 1970.[16]

- **Citation of the results from the Michigan survey in 1970:** *"It was not uncommon [in the interviews] to hear from individuals who had been to parties where a professional (doctor, nurse, scientist, inhalation therapist, researcher) had provided nitrous oxide. There also were those who work in restaurants who used the N_2O stored in tanks for the preparation of whip cream. Reports were received from people who used the gas contained in aerosol cans both of food and non-food products. At a recent rock festival nitrous oxide was widely sold for 25 cents a balloon. Contact was made with a "mystical-religious" group that used the gas to accelerate arriving at their transcendental-meditative state of choice. Although a few, more sophisticated users employed nitrous oxide-oxygen mixes with elaborate equipment, most users used balloons or plastic bags. They either held a breath of N_2O or rebreathed the gas. There were no adverse effects reported in the more than one hundred individuals surveyed."*[16]

Inhaling nitrous oxide from tanks used in automotive systems is unsafe, because the toxic gas sulfur dioxide is mixed in around 100 ppm, specifically to discourage recreational use.[34]

Neuropharmacology

The pharmacological mechanism of action of N_2O in medicine is not fully known. However, it has been shown to directly modulate a broad range of ligand-gated ion channels, and this likely plays a major role in many of its effects. It moderately blocks NMDA and β_2-subunit-containing nACh channels, weakly inhibits AMPA, kainate, $GABA_C$, and $5\text{-}HT_3$ receptors, and slightly potentiates $GABA_A$ and glycine receptors.[42] [43] It has also been shown to activate two-pore-domain K^+ channels.[44] While N_2O affects quite a few ion channels, its anesthetic, hallucinogenic, and euphoriant effects are likely caused predominantly or fully via inhibition of NMDAR-mediated currents.[42] [45] In addition to its effects on ion channels, N_2O may act to imitate nitric oxide (NO) in the central nervous system as well, and this may relate to its analgesic and anxiolytic properties.[45]

Anxiolytic effect

In behavioral tests of anxiety, a low dose of N_2O is an effective anxiolytic, and this anti-anxiety effect is associated with enhanced activity of $GABA_A$ receptors as it is partially reversed by benzodiazepine receptor antagonists. Mirroring this, animals which have developed tolerance to the anxiolytic effects of benzodiazepines are partially tolerant to N_2O.[46] Indeed, in humans given 30% N_2O, benzodiazepine receptor antagonists reduced the subjective reports of feeling "high", but did not alter psycho-motor performance, in human clinical studies.[47]

Analgesic effect

The analgesic effects of N_2O are linked to the interaction between the endogenous opioid system and the descending noradrenergic system. When animals are given morphine chronically they develop tolerance to its pain-killing effects, and this also renders the animals tolerant to the analgesic effects of N_2O.[48] Administration of antibodies which bind and block the activity of some endogenous opioids (not β-endorphin) also block the antinociceptive effects of N_2O.[49] Drugs which inhibit the breakdown of endogenous opioids also potentiate the antinociceptive effects of N_2O.[49] Several experiments have shown that opioid receptor antagonists applied directly to the brain block the antinociceptive effects of N_2O, but these drugs have no effect when injected into the spinal cord.

Conversely, α_2-adrenoceptor antagonists block the antinociceptive effects of N_2O when given directly to the spinal cord, but not when applied directly to the brain.[50] Indeed, α_{2B}-adrenoceptor knockout mice or animals depleted in norepinephrine are nearly completely resistant to the antinociceptive effects of N_2O.[51] It seems N_2O-induced release of endogenous opioids causes disinhibition of brain stem noradrenergic neurons, which release norepinephrine into the spinal cord and inhibit pain signaling.[52] Exactly how N_2O causes the release of endogenous opioid peptides is still uncertain.

Euphoric effect

In rats, N_2O stimulates the mesolimbic reward pathway via inducing dopamine release and activating dopaminergic neurons in the ventral tegmental area and nucleus accumbens, presumably through antagonization of NMDA receptors localized in the system.[53] [54] [55] [56] This action has been implicated in its euphoric effects, and notably, appears to augment its analgesic properties as well.[53] [54] [55] [56]

However, it is remarkable that in mice, N_2O blocks amphetamine-induced carrier-mediated dopamine release in the nucleus accumbens and behavioral sensitization, abolishes the conditioned place preference (CPP) of cocaine and morphine, and does not produce reinforcing (or aversive) effects of its own.[57] [58] Studies on CPP of N_2O in rats is mixed, consisting of reinforcement, aversion, and no change.[59] In contrast, it is a positive reinforcer in squirrel monkeys,[60] and is well known as a drug of abuse in humans.[61] These discrepancies in response to N_2O may reflect species variation or methodological differences.[58] Though, it is noteworthy that in human clinical studies, N_2O was found to produce mixed responses similarly to rats, reflecting high subjective individual variability.[62] [63]

Neurotoxicity

Similarly to other NMDA antagonists like ketamine, N_2O has been demonstrated to produce neurotoxicity in the form of Olney's lesions (damage to the posterior cingulate and retrosplenial cortices of the brain) in rodents upon prolonged (e.g., several hour) exposure.[64] [65] [66] [67] However, it also simultaneously exerts widespread neuroprotective effects via inhibiting glutamate-induced excitotoxicity, and it has been argued that on account of its very short duration under normal circumstances, N_2O may not share the neurotoxicity of other NMDA antagonists.[68] Indeed, in rodents, short-term exposure results in only mild injury that is rapidly reversible, and permanent neuronal death only occurs after constant and sustained exposure.[64] Moreover, Olney's lesions have never been observed in primates (including humans). However, Olney's lesions must be observed within a few hours of death, which may explain why they have not been observed in primates. After a few hours, depending on dose, the vacuoles that have appeared in the neurons resolve. If the dose is large enough to kill neurons, glial cells fill in any spaces left by the dead neurons within a short time, making it impossible to tell that neurons were even there.[69] [70] Humans cannot be exposed to nitrous oxide and killed in order to investigate whether brain injury has occurred, and in most cases, primates are not killed either. While it is then impossible to determine if brain injury does result from the use of nitrous oxide, it is most likely that it does not cause cell death because exposure is typically not long enough to do so.

Safety

The major safety hazards of nitrous oxide come from the fact that it is a compressed liquefied gas, an asphyxiation risk, and a dissociative anaesthetic. Exposure to nitrous oxide causes short-term decreases in mental performance, audiovisual ability, and manual dexterity.[71] Long term exposure can cause vitamin B_{12} deficiency, numbness, reproductive side effects (in pregnant females), and other problems (see *Recreational use* and *Biological* factors in this article).

The National Institute for Occupational Safety and Health recommends that workers' exposure to nitrous oxide should be controlled during the administration of anesthetic gas in medical, dental, and veterinary operators.[72]

Chemical/physical

At room temperature (20°C) the saturated vapor pressure is 58.5 bar, rising up to 72.45 bar at 36.4°C — the critical temperature. The pressure curve is thus unusually sensitive to temperature.[73] Liquid nitrous oxide acts as a good solvent for many organic compounds; liquid mixtures may form shock sensitive explosives.

As with many strong oxidizers, contamination of parts with fuels have been implicated in rocketry accidents, where small quantities of nitrous/fuel mixtures explode due to 'water hammer' like effects (sometimes called 'dieseling' — heating due to adiabatic compression of gases can reach decomposition temperatures).[74] Some common building materials such as stainless steel and aluminium can act as fuels with strong oxidisers such as nitrous oxide, as can contaminants, which can ignite due to adiabatic compression.[75]

There have also been accidents where nitrous oxide decomposition in plumbing has led to the explosion of large tanks.[76]

Biological

Nitrous oxide inactivates the cobalamin form of vitamin B_{12} by oxidation. Symptoms of vitamin B_{12} deficiency, including sensory neuropathy, myelopathy, and encephalopathy, can occur within days or weeks of exposure to nitrous oxide anesthesia in people with subclinical vitamin B_{12} deficiency. Symptoms are treated with high doses of vitamin B_{12}, but recovery can be slow and incomplete.[77] People with normal vitamin B_{12} levels have stores to make the effects of nitrous oxide insignificant, unless exposure is repeated and prolonged (nitrous oxide abuse). Vitamin B_{12} levels should be checked in people with risk factors for vitamin B_{12} deficiency prior to using nitrous oxide anesthesia.

A study of workers[78] and several experimental animal studies[79] [79] [80] [81] indicate that adverse reproductive effects for pregnant females may also result from chronic exposure to nitrous oxide.

Environmental

N_2O is a greenhouse gas with tremendous global warming potential (GWP). When compared to carbon dioxide (CO_2), N_2O has 310 times the ability to trap heat in the atmosphere.[82] N_2O is produced naturally in the soil during the microbial processes of nitrification and denitrification.

The United States of America signed and ratified the United Nations Framework Convention on Climate Change (UNFCC [83]) in 1992, agreeing to inventory and assess the various sources of greenhouse gases that contribute to climate change.[84] The agreement requires parties to “develop, periodically update, publish and make available…national inventories of anthropogenic emissions by sources and removals by sinks of all greenhouse gases not controlled by the Montreal Protocol, using comparable methodologies…”.[85] In response to this agreement, the U.S. is obligated to inventory anthropogenic emissions by sources and sinks, of which agriculture is a key contributor. In 2008, agriculture contributed 6.1% of the total U.S. greenhouse gas emissions and cropland contributed nearly 69% of total direct nitrous oxide (N_2O) emissions. Additionally, estimated emissions from agricultural soils were 6% higher in 2008 than 1990.[84]

According to 2006 data from the United States Environmental Protection Agency, industrial sources make up only about 20% of all anthropogenic sources, and include the production of nylon, and the burning of fossil fuel in internal combustion engines. Human activity is thought to account for 30%; tropical soils and oceanic release account for 70%.[86] However, a 2008 study by Nobel Laureatte Paul Crutzen suggests that the amount of nitrous oxide release attributable to agricultural nitrate fertilizers has been seriously underestimated, most of which would presumably come under soil and oceanic release in the Environmental Protection Agency data.[87] Atmospheric levels have risen by more than 15% since 1750.[88] Nitrous oxide also causes ozone depletion. A new study suggests that N_2O emission currently is the single most important ozone-depleting substance (ODS) emission and is expected to remain the largest throughout the 21st century.[89] [90]

Legality

In the United States, possession of nitrous oxide is legal under federal law and is not subject to DEA purview.[91] It is, however, regulated by the Food and Drug Administration under the Food Drug and Cosmetics Act; prosecution is possible under its "misbranding" clauses, prohibiting the sale or distribution of nitrous oxide for the purpose of human consumption.

Many states have laws regulating the possession, sale, and distribution of nitrous oxide. Such laws usually ban distribution to minors or limit the amount of nitrous oxide that may be sold without special license. For example, in the state of California, possession for recreational use is prohibited and qualifies as a misdemeanor.[92]

In New Zealand, the Ministry of Health has warned that nitrous oxide is a prescription medicine, and its sale or possession without a prescription is an offense under the Medicines Act.[93] This statement would seemingly prohibit all non-medicinal uses of the chemical, though it is implied that only recreational use will be legally targeted.

In India, for general anaesthesia purposes, nitrous oxide is available as Nitrous Oxide IP. India's gas cylinder rules (1985) permit the transfer of gas from one cylinder to another for breathing purposes. This law benefits remote hospitals, which would otherwise suffer as a result of India's geographic immensity. Nitrous Oxide IP is transferred from bulk cylinders (17,000 liters capacity gas) to smaller pin-indexed valve cylinders (1,800 liters of gas), which are then connected to the yoke assembly of Boyle's machines. Because India's Food & Drug Authority (FDA-India) rules state that transferring a drug from one container to another (refilling) is equivalent to manufacturing, anyone found doing so must possess a drug manufacturing license.

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External links

- Occupational Safety and Health Guideline for Nitrous Oxide (http://www.osha.gov/SLTC/healthguidelines/nitrousoxide/recognition.html)
- Paul Crutzen Interview (http://www.vega.org.uk/video/programme/111) Freeview video of Paul Crutzen Nobel Laureate for his work on decomposition of ozone talking to Harry Kroto Nobel Laureate by the Vega Science Trust.
- National Pollutant Inventory – Oxide of nitrogen fact sheet (http://www.npi.gov.au/database/substance-info/profiles/67.html)
- National Institute for Occupational Safety and Health – Nitrous Oxide (http://www.cdc.gov/niosh/topics/nitrousoxide/)
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- Dental Fear Central article on the use of nitrous oxide in dentistry (http://www.dentalfearcentral.org/help/sedation-dentistry/laughing-gas/)

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