Minimum Alveolar Concentrations of Noble Gases, Nitrogen, and Sulfur Hexafluoride in Rats: Helium and Neon as Nonimmobilizers (Nonanesthetics)

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We assessed the anesthetic properties of helium and neon at hyperbaric pressures by testing their capacity to decrease anesthetic requirement for desflurane using electrical stimulation of the tail as the anesthetic endpoint (i.e., the minimum alveolar anesthetic concentration [MAC]) in rats. Partial pressures of helium or neon near those predicted to produce anesthesia by the Meyer-Overton hypothesis (approximately 80–90 atm), tended to increase desflurane MAC, and these partial pressures of helium and neon produced convulsions when administered alone. In contrast, the noble gases argon, krypton, and xenon were anesthetic with mean MAC values of (± SD) of 27.0 ± 2.6, 7.31 ± 0.54, and 1.61 ± 0.17 atm, respectively. Because the lethal partial pressures of nitrogen and sulfur hexafluoride overlapped their anesthetic partial pressures, MAC values were determined for these gases by additivity studies with desflurane. Nitrogen and sulfur hexafluoride MAC values were estimated to be 110 and 14.6 atm, respectively. Of the gases with anesthetic properties, nitrogen deviated the most from the Meyer-Overton hypothesis. **Implications:** It has been thought that the high pressures of helium and neon that might be needed to produce anesthesia antagonize their anesthetic properties (pressure reversal of anesthesia). We propose an alternative explanation: like other compounds with a low affinity to water, helium and neon are intrinsically without anesthetic effect.

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Previous work documents that the noble gases helium and neon have little or no anesthetic effect (1). In mammals, the application of helium at partial pressures near those predicted by the Meyer-Overton hypothesis to produce anesthesia (approximately 100 atm) (1,2) causes convulsions rather than anesthesia. The lack of anesthesia (and even pressure reversal of anesthesia as measured by the righting reflex) and convulsant effects of high-pressure helium are commonly thought to be due to the influence of high pressure *per se* rather than any particular physical-chemical property of helium (1–5).

We suggest an alternative possibility. We recently identified nonimmobilizer (also called nonanesthetic) inhaled compounds. Nonimmobilizers are compounds that are not anesthetic (as measured by response to noxious stimuli) when administered alone, and that do not decrease the requirement (as measured by the minimum alveolar anesthetic concentration [MAC] required to eliminate movement in 50% of subjects exposed to a noxious stimulus) for conventional anesthetics (6–10). Like helium, nonimmobilizers produce convulsions rather than anesthesia in rats at partial pressures near those predicted by the Meyer-Overton hypothesis to be anesthetic. Moreover, the nonimmobilizers are similar to helium and neon in that they have a low affinity to water (6–12) and, typically, have much smaller aqueous/gas partition coefficients than inhaled anesthetics. However, in contrast to helium, these nonimmobilizer volatile compounds may exert their actions at partial pressures less than 1 atm.

Thus, an alternative view of the findings summarized above is that helium does not fail to cause anesthesia because of the associated application of high

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pressure, but rather because it is a nonimmobilizer. These possibilities animated our decision to determine the anesthetic and convulsant properties of helium and other (especially noble) gases using noxious stimuli as the anesthetic endpoint (MAC).

Methods

With approval from our institutional committees on animal research, we studied the anesthetic properties or lack thereof, of seven gases in adult specific pathogen-free Sprague-Dawley male rats (274–370 g; Charles River Laboratories, Saratoga, CA). Each animal was caged individually and had continuous access to standard rat chow and tap water before the study. Gases were purchased from Altair/Praxair (San Ramon, CA) or Air Products (Allentown, PA) and were of the highest purity available (all >99.99% pure). Desflurane was donated by Ohmeda Pharmaceutical Products Division (Liberty Corner, NJ).

Rats were prepared in individual plastic cylinders before they were placed in a hyperbaric chamber, as described for previous studies (6,7). We secured the tail to an extension of the cylinder, inserted a rectal temperature probe, and placed four pairs of subcutaneous stimulating needle electrodes into the tail. Except for its secured tail, the rat was free to move (6,7). Stimulating electrodes were not placed in animals used solely to test for convulsive thresholds. Each rat, enclosed in its individual plastic cylinder, was placed into either a 3.4-L clear plastic pressure chamber (capable of holding two rats) or a 20-L stainless steel pressure chamber (capable of holding four or five rats) with a Plexiglas viewing port at the head end of the chamber (6,13). The smaller hyperbaric chamber was used when drugs were in limited supply and/or expensive (e.g., xenon) and when only relatively low hyperbaric pressures (several atmospheres) were required. The larger, stainless steel hyperbaric chamber was used when experiments demanded high (approximately 80 atm) pressures (e.g., helium, neon). Each hyperbaric chamber had connections that powered a circulation fan that mixed gases through a CO_2 absorber and allowed for electrical stimulation of the tail and monitoring of rectal temperatures. In the smaller pressure chamber, we achieved temperature control by applying ice bags or heat lamps to the outside of the chamber. The large hyperbaric chamber was equipped with internal and external water-circulating temperature-control coils. Rectal temperatures were typically maintained between 36.5 and 39.0°C but were more difficult to control with the high-pressure helium and neon experiments and reached a low of 34.7°C and a high of 39.9°C. Ports in both chambers allowed introduction and sampling of gases and measurement of chamber pressure. Before the introduction of test gases, the chamber was flushed with oxygen for 10 min (chamber concentration at 1 atm >98% O_2).

After flushing the large hyperbaric chamber with oxygen, we added helium, neon, nitrogen, or argon at a rate that increased pressure in the chamber by 2 atm/min. Each animal was continuously examined for a convulsion, defined by strong contractions of muscles over most of the body with the muscles alternately contracting and relaxing. We noted the pressure at which the first convulsion occurred or the maximal pressure achieved without eliciting a convulsion.

Except for helium and neon, each gas was tested alone for its ability to produce anesthesia (defined by an absence of motor response to electrical stimulation of the tail) over a range of partial pressures. If the gas alone did not produce anesthesia or if the partial pressure producing anesthesia minimally differed from that causing death, additivity studies were performed to determine whether the gas decreased the requirement (MAC) for desflurane.

For the additivity studies, control MAC values for desflurane were determined at atmospheric pressure in the hyperbaric chamber using electrical stimulation (14) as the anesthetic endpoint. At the end of the control desflurane MAC determination, all animals were nonresponsive at the highest desflurane concentration tested, and the chamber was then flushed with oxygen to decrease the desflurane concentration to approximately 50% of the control MAC value. Return of spontaneous or lightly stimulated movement was documented for each animal. The chamber was then sealed, and the test gas was increased to a predetermined target pressure, typically at a rate of 2 atm/min, and the MAC for desflurane was redetermined. If a rat exhibited purposeful movement in response to the electrical stimulus (15-volt, 50-Hz, biphasic, 6.5-ms/pulse electrical stimulus applied for up to 1 min) after equilibration (typically 20 min), desflurane partial pressure in the hyperbaric chamber was increased by approximately 20%, and the rat was retested after a further 20-min equilibration period. To introduce desflurane into the chamber at high pressures, liquid desflurane was injected into a small auxiliary chamber at 1 atm, and the auxiliary chamber was then pressurized with the test gas or oxygen and opened to the main chamber (6). After a negative response, the animal was retested with a more proximal pair of stimulating electrodes to exclude a false-negative response caused by tissue damage or electrode displacement.

After each determination of the response to electrical stimulation, a chamber gas sample was obtained for analysis of O_2, which was controlled at 0.5–1.5 atm.

Table 1. Anesthetic Potencies (MAC Values) of Noble Gases, N_2, and SF_6

Compound	N	Control desflurane (atm)[a]	Experimental desflurane (atm)[b]	PP_A (atm)	MAC_A (atm)
Helium	8	0.074 ± 0.0068	0.0884 ± 0.0174*	86.0 ± 1.3	No anesthesia
Neon	11	0.0659 ± 0.0083	0.0740 ± 0.0121	83.6 ± 2.7	No anesthesia
Argon	5				27.0 ± 2.6
Krypton	4				7.31 ± 0.54
Xenon	4				1.61 ± 0.17
Nitrogen	5				46.5 ± 8.4
Nitrogen	15	0.0729 ± 0.0073	0.0632 ± 0.0052	14.4 ± 0.3	108 ± 14.0
Nitrogen	16	0.0714 ± 0.0098	0.0553 ± 0.0094	25.9 ± 0.8	115 ± 25.1
Nitrogen	4	0.0776 ± 0.0104	0.0612 ± 0.0117	38.0 ± 0.4	180 ± 42
Sulfur hexafluoride	1				12.0[a]
Sulfur hexafluoride	10	0.0698 ± 0.0014	0.0425 ± 0.0028	5.65 ± 0.13	14.6 ± 1.3

Values are expressed as means ± SD.
[a] Four of five animals died at a partial pressure of 11.1 atm.
* Significantly different from control ($p = 0.018$).
Minimum alveolar anesthetic (MAC) values of desflurane are given without (control) and with (experimental) the test gas. If no values are given for desflurane MAC, the MAC for the test gas was determined alone in the absence of desflurane.
PP_A = partial pressure of the test gas during the additivity studies, MAC_A = MAC of the gaseous agent when administered alone, or estimated MAC of the gaseous agent assuming additive anesthetic effects with desflurane.

Chamber pressures were measured by using calibrated aneroid gauges. Desflurane was quantified by using gas chromatography (6).

For gases that produced anesthesia when administered alone, we calculated MAC values for each animal as the average of the partial pressures that just permitted and just prevented movement. The anesthetic effect of the test gas in the additivity studies was calculated from the decrease in desflurane MAC resulting from the presence of the test gas. Failure to find a significant ($P < 0.05$ via paired t-test) decrease in desflurane MAC in the presence of the test gas indicated an absence of any anesthetic effect of the test gas. For additivity studies of nitrogen and sulfur hexafluoride, MAC values were calculated as the average of the applied partial pressures for each gas divided by 1 minus the ratio of desflurane MAC in the presence of nitrogen (or sulfur hexafluoride) divided by the MAC of desflurane in the absence of the test gas (6). The standard deviations for the calculated MAC values of nitrogen or sulfur hexafluoride for the additivity studies were estimated by multiplying the calculated MAC value by the square root of the sum of the squares of the ratios of the standard deviation of the control and experimental desflurane MAC values divided by their respective mean MAC values.

Results

With an increase in pressure at a rate of 2 atm/min, convulsions occurred at 84.6 ± 22.2 atm of helium ($n = 10$) and at 91.3 ± 7.0 atm of neon ($n = 8$) [mean ± SD]. No other gases produced convulsions, although some rats exposed to nitrogen and argon exhibited transient tremors and head-bobbing.

MAC values for helium and neon could not be determined because the rats maintained spontaneous activity at the highest pressures examined (approximately 100 atm) and eventually exhibited convulsions. MAC values were quantitated for the remaining five gases (Table 1). However, the MAC value for sulfur hexafluoride (12.0 atm) was successfully determined (i.e., recovery occurred after testing of highest partial pressure) in only one of five rats because the remaining rats died at sulfur hexafluoride partial pressures of approximately 11 atm before movement was suppressed (Table 1). Similarly, the MAC value measured for nitrogen by itself (46.5 ± 8.4 atm) approximated the 50% lethal dose (53.6 atm) for nitrogen measured in these same animals at slightly higher pressures. Accordingly, MAC values for sulfur hexafluoride and nitrogen were determined by additivity studies with desflurane.

Average control desflurane MAC values ranged from 0.0659 to 0.0776 atm (Table 1). For the additivity studies, desflurane was initially added to approximately 50% of the control MAC (i.e., 0.03–0.04 atm desflurane) and allowed to equilibrate 20–30 min before introduction of the test gas. This background concentration of desflurane prevented the convulsions seen with helium or neon administered alone, but intermittent excitatory activity (e.g., tremors, head-bobbing) still occurred at high pressures of these drugs. Neither helium nor neon (at approximately 85 atm) lowered the anesthetic requirement for desflurane, which indicates that these compounds are devoid of anesthetic properties. Instead, helium significantly ($P = 0.018$) increased desflurane MAC by 19%, and there was a nonsignificant trend ($P = 0.12$) for neon to increase desflurane MAC by 12% (Table 1).

Table 2. Meyer-Overton Relationships for Noble Gases, H_2, N_2, and SF_6

Compound	Rat MAC (atm)	Predicted rat MAC (atm)[a]	Water/gas part coeff (35°C)	Oil/gas part coeff (37°C)	MAC × oil/gas part coeff (atm)
Helium	No anesthesia	114	0.0085	0.016	No anesthesia
Neon	No anesthesia	95.8	0.0098	0.019	No anesthesia
Argon	27.0	14.0	0.026	0.13	3.51
Krypton	7.31	4.55	0.045	0.4	2.92
Xenon	1.61	1.01	0.075	1.8	2.90
Hydrogen	ND	36.4	0.017	0.05	ND
Nitrogen[c]	108	26.4	0.013	0.069	7.45
Sulfur hexafluoride[c]	14.6	7.0	0.0042[b]	0.26	3.80

Values for the partition coefficients were taken from Reference 11, except for the value of the oil/gas partition coefficient of nitrogen at 37°C, which was listed incorrectly as 0.66 in Reference 11. Instead, an average of two values (0.069) was taken from Reference 12.

ND = not determined, part coeff = partition coefficient.

[a] Based on the assumption that the minimum alveolar anesthetic concentration (MAC) × (oil/gas partition coefficient) = 1.82 atm (29).

[b] At 37°C.

[c] Best estimates taken from Table 1.

Nitrogen MAC, quantitated at three different nitrogen pressures by additivity studies with desflurane, was two- to fourfold greater than the MAC measured with nitrogen alone (Table 1).

Discussion

Our finding of helium-induced convulsions at a pressure of 84.6 ± 22.2 atm in Sprague-Dawley male rats confirms reports that applied similar compression rates (the convulsive threshold varies with the rate of compression) (15). We found neon-induced convulsions at 91.3 ± 7.0 atm, a pressure lower than that previously reported in mice (130 atm) (3), recognizing that we used a higher compression rate (2 atm/min) than that used in the mouse studies (1.25 atm/min) (3).

Both helium and neon may be classified as nonimmobilizers. Neither produced anesthesia alone, neither decreased the MAC for desflurane (Table 1), and both caused convulsions. Indeed, both helium and neon (at approximately 85 atm) increased (statistically significant difference for helium) desflurane MAC (Table 1), consistent with previous data that suggested the pressure reversal effect of high-pressure helium (3,13). However, these pressure reversal studies of nitrous oxide and isoflurane in mice used the righting reflex as the anesthetic endpoint, demonstrating approximately a 40% increase in anesthetic requirement at helium pressures of approximately 85 atm (13). One other study used noxious stimulation (electrical stimulus to the tail of a mouse), rather than righting reflex, as the anesthetic endpoint to study the pressure reversal of anesthesia. Similar to our findings, 75 atm of helium did not antagonize the analgesia produced by 1.2 atm of nitrous oxide (16). Information on the administration of neon to rodents is limited (3), and no previous studies have examined the anesthetic properties of neon using MAC (i.e., noxious stimulation) as the anesthetic endpoint. In the present experiments, high pressures of neon produced a nonsignificant 12% increase in desflurane MAC in the rat.

Like other nonimmobilizers, helium and neon do not cause anesthesia and do produce convulsions near partial pressures predicted to produce anesthesia by the Meyer-Overton rule (Table 2) (7–9). Like most other nonimmobilizers, helium and neon also have relatively low aqueous/gas partition coefficients (Table 2), which suggests a role of drug affinity to water in determining anesthetic potency. However, the aqueous/gas partition coefficient alone cannot be used to separate anesthetics from nonimmobilizers (8,9).

The definition of a nonimmobilizer uses movement versus nonmovement in response to a noxious stimulus as the anesthetic endpoint (6–9). Because nonimmobilizers may provide other components of anesthesia, e.g., amnesia (18), it is more appropriate to refer to them as nonimmobilizers than as nonanesthetics (19). The view derived from the present experiments—that helium and neon are nonimmobilizers—may differ quantitatively from previous studies that investigated the anesthetic properties of helium and neon at high pressures (3,13,20). For example, as indicated above, approximately 85 atm of helium increases the righting reflex 50% effective dose (ED_{50}) for nitrous oxide by approximately 40%, whereas we found only a 19% increase in MAC. These quantitative differences may result, in part, from the use of different anesthetic endpoints (response to noxious stimuli versus the righting reflex).

Most previous studies of noble gases used the righting reflex as the measure of anesthetic potency (Table 3). Our data for the MAC values of argon, krypton, and xenon in rats give values 60%–80% greater than those required to suppress the righting reflex in mice (Table 3). The values for the righting reflex ED_{50} compared with MAC are probably smaller

Table 3. Anesthetic Potencies of Noble Gases, H_2, N_2, and SF_6 in Rodents

Compound	MAC (atm) in rats (present study)	Righting reflex[a] ED_{50} (atm) in mice	Rat MAC to mouse righting reflex	Reference
Helium	No anesthesia	No anesthesia	No anesthesia	3
Neon	No anesthesia	No anesthesia	No anesthesia	3
Argon	27.0	15.2	1.78	21
Krypton	7.31	4.5	1.62	21
Hydrogen	ND	128.8	ND	22
Xenon	1.61	0.95	1.70	23
Nitrogen	108	32.5	3.38	23
Sulfur hexafluoride	14.6	6.9	2.12	23

MAC = minimum alveolar anesthetic concentration, ND = not determined, ED_{50} = 50% effective doses.
[a] Righting reflex is equated to the rolling response, typically measured by placing animals in a rotating cage.

because the righting reflex requires a sustained and coordinated muscular activity, whereas the response to a noxious stimulus requires only a brief and minimally coordinated movement. This finding is consistent with previous rodent studies of other inhaled anesthetics, which demonstrated a similar ratio of MAC to the righting reflex ED_{50} (24–26). Unlike krypton and argon, xenon MAC has been measured in higher mammals [human 0.71 atm (17), monkey 0.95 atm (27), dog 1.19 atm (28)], with these values tending to be lower than MAC in rats. The products of the oil/gas partition coefficient × MAC in rats for argon, krypton, and xenon vary between 2.90 and 3.51 atm, values not markedly different from the product of 1.82 ± 0.56 for conventional anesthetics that obey the Meyer-Overton hypothesis (29).

Hydrogen was not examined because of safety concerns regarding mixtures of hydrogen and oxygen at high pressures. However, the influence of high pressures of hydrogen has been previously examined by others (22,30). Electroencephalographic studies in rhesus monkeys demonstrated that convulsions of a grand mal type may occur when hydrogen pressures reach 60–100 atm (30). Tremors in mice were observed starting at 60 atm, with approximately 10% of mice eventually convulsing. At higher pressures of hydrogen, loss of righting reflex in mice occurred at 128.8 ± 7.3 atm (22,30). In contrast, electroencephalographic measurements in rhesus monkeys showed no evidence of deep narcosis at hydrogen pressures up to 110 atm (30). The convulsive properties of hydrogen at a pressure near that predicted to produce anesthesia by the Meyer-Overton hypothesis (Table 2) are consistent with the classification of hydrogen as a nonimmobilizer. Nevertheless, the ability of hydrogen to abolish the righting reflex in mice is indicative of an anesthetic effect, and if the ratio of the MAC to the righting reflex (2) (Table 3) for hydrogen is similar to that for other anesthetic gases, the MAC of hydrogen in rats would be approximately 250 atm, or 8 times the predicted MAC (Table 2).

For sulfur hexafluoride and nitrogen, the closeness of their MAC values when tested alone to their lethal pressures compromised our ability to distinguish anesthetic from toxic effects. Accordingly, MAC values for these two gases were determined by additivity measurements with desflurane. The MAC for sulfur hexafluoride is approximately twice the mouse righting reflex ED_{50} (Table 3), and this MAC does not markedly deviate from that predicted by the Meyer-Overton hypothesis (Table 2). The rat MAC for sulfur hexafluoride exceeds by approximately threefold the MAC measured in dogs (4.9 atm) (31), but the MAC in dogs may be artificially low because the use of repeated electrical stimulation applied to a single pair of electrodes (6,31) may damage nerves and result in an apparent decrease in the intensity of stimulation.

The most reliable of the nitrogen MAC measurements (Table 1) are probably the values obtained by desflurane additivity studies with the two background nitrogen pressures of approximately 14 and approximately 26 atm, which gave consistent nitrogen MAC values of 108 and 115 atm, values approximately threefold greater than those needed to suppress the mouse righting reflex (Table 3). The only other attempt to measure nitrogen MAC in mammals was in (two) dogs, which continued to respond to noxious stimuli at 43.5 atm of nitrogen (31). If the MAC of nitrogen is approximately 110 atm, then the product of its oil/gas partition coefficient × MAC equals 7.6, making it less potent than predicted by the Meyer-Overton hypothesis (Table 2).

In the additivity studies of sulfur hexafluoride and nitrogen with desflurane, we assumed that the anesthetic effects are additive (e.g., 0.5 MAC of one drug plus 0.5 MAC of another drug produces the same effect as 1.0 MAC of either drug). Although this is usually the case for conventional inhaled anesthetics (32), sometimes inhaled anesthetic effects are nonadditive (33). This assumption bears on our previous argument that an affinity for water is crucial to the production of anesthesia as defined by MAC (19). If the MAC value we measured for sulfur hexafluoride is correct, then this compound is an anomaly, because the water/gas partition coefficient of sulfur hexafluoride is approximately half the helium and neon values

(Table 2). Such an anomaly may undermine the argument regarding the role of aqueous affinity as essential to a molecule's capacity to produce anesthesia and may provide guidance in the search for the properties that determine anesthetic potency.

We examined the anesthetic properties of five noble gases and nitrogen and sulfur hexafluoride in rats using response to noxious stimuli (MAC) as the anesthetic endpoint. Helium and neon had no anesthetic properties and produced convulsions when administered alone at the high pressures predicted to be anesthetic by the Meyer-Overton hypothesis. Helium and neon tended to increase the MAC for desflurane. MAC values for the remaining compounds were measurable and were twofold greater than mouse righting reflex ED_{50} values. Of the gases that had anesthetic properties, nitrogen deviated the most from the Meyer-Overton hypothesis.

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