Nuclear Spin Attenuates the Anesthetic Potency of Xenon Isotopes in Mice

Implications for the Mechanisms of Anesthesia and Consciousness

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ABSTRACT

Background: Xenon is an elemental anesthetic with nine stable isotopes. Nuclear spin is a quantum property which may differ among isotopes. Xenon 131 (^{131}Xe) has nuclear spin of 3/2, xenon 129 (^{129}Xe) a nuclear spin of 1/2, and the other seven isotopes have no nuclear spin. This study was aimed to explore the effect of nuclear spin on xenon anesthetic potency.

Methods: Eighty C57BL/6 male mice (7 weeks old) were randomly divided into four groups, xenon 132 (^{132}Xe), xenon 134 (^{134}Xe), ^{131}Xe, and ^{129}Xe groups. Due to xenon's low potency, loss of righting reflex ED50 for mice to xenon was determined with 0.50% isoflurane. Loss of righting reflex ED50 of isoflurane was also measured, and the loss of righting reflex ED50 values of the four xenon isotopes were then calculated. The exact polarizabilities of the isotopes were calculated.

Results: Combined with 0.50% isoflurane, the loss of righting reflex ED50 values were 15 ± 4%, 16 ± 5%, 22 ± 5%, and 23 ± 7% for ^{132}Xe, ^{134}Xe, ^{131}Xe, and ^{129}Xe, respectively. For xenon alone, the loss of righting reflex ED50 values of ^{132}Xe, ^{134}Xe, ^{131}Xe, and ^{129}Xe were 70 ± 4%, 72 ± 5%, 99 ± 5%, and 105 ± 7%, respectively. Four isotopes had a same exact polarizability of 3.60 Å^3.

Conclusions: Xenon isotopes with nuclear spin are less potent than those without, and polarizability cannot account for the difference. The lower anesthetic potency of ^{129}Xe may be the result of it participating in conscious processing and therefore partially antagonizing its own anesthetic potency. Nuclear spin is a quantum property, and our results are consistent with theories that implicate quantum mechanisms in consciousness. **(ANESTHESIOLOGY 2018; 129:271-7)**

THE mechanism by which general anesthetics cause reversible loss of consciousness, and by which the brain produces consciousness, are both unknown.[1] Meyer and Overton showed that anesthetic potency correlated with solubility in nonpolar olive oil, which was taken to imply that anesthetics act in lipid membranes.[2] However, proteins were found to mediate membrane excitability, and Franks and Lieb[3] found that anesthetics bind and act in nonpolar, lipid-like regions within proteins, using the membrane-free light-emitting protein enzyme luciferase. Accordingly, anesthetics are recognized to act directly in proteins, still consistent with Meyer-Overton.[3] These studies focused on intermolecular actions of general anesthetics with nonpolar lipid and nonpolar regions within proteins. The intermolecular attractions are due to weak, quantum-level van der Waals London force couplings between anesthetic electron shells and electron clouds of nonpolar groups within particular proteins, *e.g.*, π-electron resonance groups of aromatic amino acid rings.[4] Craddock *et al.*[4] point out that Meyer-Overton defines a quantum-friendly environment for electron cloud dipoles and spin processes, and propose that anesthetics act in quantum channels in brain microtubules to prevent consciousness. However, the effect of the atomic nucleus on the anesthetic potencies of general anesthetics is unknown. The atomic nucleus shows some

What We Already Know about This Topic

- Xenon is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist. The interaction of xenon with the NMDA receptor is determined by quantum-level van der Waals London forces between the electron shells of xenon and the electron clouds of nonpolar regions of the NMDA receptor.
- In addition to the van der Waals forces, several xenon isotopes have nuclear spin. Whether the quantum property of nuclear spin affects the potency of xenon is not known.

What This Article Tells Us That Is New

- The potency of two xenon isotopes with nuclear spin, xenon 129 and xenon 131, is less than the potency of two xenon isotopes, xenon 132 and xenon 134, that do not have nuclear spin. This difference in potency cannot be explained, either by differences in outer electron shells (there are none) or the variations in atomic mass.
- The results suggest that some of the effects of xenon on consciousness may be mediated by quantum mechanisms.

Corresponding article on page 228. N.L., D.L., L.Y., and H.T. contributed equally to this article.

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quantum features, including spin, a fundamental feature of the universe. Exploring the effects of nuclear spin of general anesthetics may help reveal quantum mechanisms in anesthetic action and consciousness. Xenon is an elemental gaseous anesthetic[5] that has nine stable isotopes. Xenon 129 (^{129}Xe) has a nuclear spin of 1/2 and xenon 131 (^{131}Xe) of 3/2, and the other seven isotopes have no nuclear spin (0).[6] Xenon isotopes have differences in nuclear spin, making them suitable to study the effect of the atomic nucleus on anesthetic action. We thus postulated that xenon isotopes might have different anesthetic potencies.

In order to test our hypothesis in this study, we aimed to measure the anesthetic potencies of ^{129}Xe, ^{131}Xe, xenon 132 (^{132}Xe), and xenon 134 (^{134}Xe) in mice. There are two classical methods to measure anesthetic potency in animals: loss of righting reflex and tail clipping. The concentrations of anesthetics that are necessary to produce loss of consciousness in humans are similar to those needed to induce loss of righting reflex in animals[7]; therefore, loss of righting reflex is a correlate of consciousness, while tail clipping is a measure of immobility.[8] In order to match consciousness, we aimed to determine loss of righting reflex for mice to xenon isotopes in this study. In order to compare the different effects of outer electron shells of xenon isotopes on their anesthetic potencies, the exact polarizabilities of the four isotopes were also calculated.

Materials and Methods

Animals

C57BL/6 male mice (aged 7 weeks) were ordered from Hunan SJA Laboratory Animal Co., Ltd. (SCXK[xiang]2016-0002; China). All animal procedures were approved by the Institutional Animal Care and Use Committee (S164) at Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. The study protocol was designed according to the recommendations of the Helsinki convention for the use and care of animals. In all experiments, mice were not in a great deal of pain and were not euthanized.

Reagents

^{129}Xe, ^{131}Xe, ^{132}Xe, and ^{134}Xe were made in Georgia, and we purchased them from NUKEM Isotopes Imaging GmbH (Germany) with purity all greater than 99.99% and abundance of 93.5%. Isoflurane was purchased from Abbott Laboratories Co., Ltd. (USA).

Study Design

In this study, we chose four isotopes: ^{129}Xe, ^{131}Xe, ^{132}Xe, and ^{134}Xe. ^{132}Xe and ^{134}Xe were chosen for controls because both have no nuclear spin. We aimed to determine loss of righting reflex for mice to each isotope and then calculate the corresponding values of loss of righting reflex ED50 in this study. Loss of righting reflex ED50 of xenon is as high as 95% in mice.[9] Under normobaric conditions, it is difficult to administer more than 70% xenon to determine loss of righting reflex ED50 because it would make the animals at risk of hypoxia. Therefore, a measurement of anesthetic potency of xenon would require either hyperbaric conditions to maintain an adequate partial pressure of oxygen,[9] or the combination of xenon with another potent anesthetic under normobaric conditions.[10] Because hyperbaric xenon may cause inadequate respiration or apnea to the animals,[11] in this study we determined the loss of righting reflex ED50 of xenon by combining it with isoflurane.

Determination of Loss of Righting Reflex for Mice to the Combination of Xenon with Isoflurane

According to a computer-generated random number table, 80 mice were divided into four groups, ^{129}Xe, ^{131}Xe, ^{132}Xe, and ^{134}Xe groups, with 20 mice in each group. According to the method described by Miller *et al.*[9] to determine ED50 of xenon in mice, 20 mice in each group would be powerful enough to determine ED50 in this study. We used a plastic mesh chamber of 6 l capable of simultaneously holding 20 mice in isolated cells to determine loss of righting reflex for mice to xenon in this study. The chamber was designed to test capably 20 mice in a group simultaneously. A powerful electrical fan was fixed in the chamber to ensure adequate mixing of the gases. The chamber was connected to an isoflurane vaporizer and oxygen source. A daily gas leak test in the chamber and associated tubing was performed by increasing the within-chamber air pressure with pure oxygen to 10 mmHg and then immersing the entire system in a water bath. After 20 mice were placed in the chamber, the chamber was sealed and gas leak was tested. Loss of righting reflex was accomplished using stepwise incremental increases in the concentration of xenon isotope. At first, 0.50% isoflurane combined with pure oxygen from the vaporizer was introduced into the chamber at a rate of 800 ml/min. A concentration of 0.50% of isoflurane was maintained for 1 h in the tightly sealed chamber, and loss of righting reflex was tested by an experimenter who was blinded to isotope type. After the first loss of righting reflex testing, 150 ml xenon was then slowly injected into the chamber with a syringe to increase the concentration of xenon to 2.5%. The injection time was about 8 min to ensure the pressure within the chamber did not exceed 2 mmHg. Mice consume oxygen, and it is estimated that 150 ml oxygen are consumed by 20 mice in 8 min. After injection, xenon concentration was equilibrated for 15 min. During the equilibration, pure oxygen was slowly introduced into the chamber to compensate the amount of oxygen consumed by the mice. In this way, the concentration of xenon was maintained constant within the chamber. After equilibration, loss of righting reflex was tested immediately. Concentration of xenon was increased by 2.5% until successful loss of righting reflex was observed. Isoflurane,

oxygen, and carbon dioxide concentrations were continuously monitored using an infrared gas monitor (PM8050; Drägerwerk, Germany), calibrated just before each use according to the manufacturer's instructions. The sample gas was returned to the chamber after analysis. Within the chamber, carbon dioxide was maintained at less than 1% by using carbon dioxide absorbent, and the temperature was maintained at 36.0 ± 0.2°C. The chamber pressure and temperature were also monitored continuously. For temperature maintenance, the mice were warmed with a heat lamp. After any experiment, mouse rectal temperature was measured immediately. Rectal temperature at 35.0 ± 0.2°C was regarded as normal. The pressure in the chamber was maintained at a range of 0 to 2 mmHg. A tank containing 5% isoflurane in pure oxygen was available. If isoflurane concentration within the chamber reduced to 0.49% due to isoflurane metabolized, the amount of isoflurane needed to keep 0.50% of isoflurane in the chamber was calculated, and the gas of the amount of isoflurane was drawn from the tank and was then introduced into the chamber to increase isoflurane concentration to 0.50%. In this way, the concentration of isoflurane within the chamber was controlled at 0.50 ± 0.01%. Only one experimenter who did not participate in determining righting response knew which xenon isotope was used in each experiment. The other experimenters were blinded.

Xenon Concentration Determination

Because the chamber was tightly sealed and the pressure within the chamber changed at a range of 0 to 2 mmHg, the concentration of xenon within the chamber was guaranteed to be constant. However, the accurate concentration of xenon within the chamber was verified. After each experiment of measurement of loss of righting reflex of any xenon isotope, a gas sample was drawn from the sealed chamber. The concentration of xenon was measured by gas chromatography/mass spectrometry in direct injection mode (without sample pretreatment). The gas chromatography/mass spectrometry system consisted of an Agilent 5973N spectrometer interfaced with an Agilent 6890 gas chromatograph (Agilent Technologies Inc., USA). Gases were separated with a HP-PLOT-Molesieve-5 Å, 30 m, 0.32 mm, 0.25 μm ID molecular sieve column (Agilent Technologies Inc.). The column temperature was 100°C. The split ratio was 50:1. The volume of the sample loop was 5 ml. The injector temperature was 120°C. The sample volume was 50 μl. The driving gas was helium (0.92 ml/min). The electrospray ionization temperature was 230°C, and the quadrupole temperature was 150°C. The other optimized parameters were ionization energy of 70 eV, emission current of 40 mA, cathode voltage of 27 mV, focus voltage of 85 mV, and lens compensation of 20 V.

Standardization of xenon isotope gas was the volumes of pure xenon gas from NUKEM Isotopes Imaging GmbH (Germany). Scanning ions were mass/charge 132, 134, 131, and 129, respectively. Scanning residence time was 100 ms. Peak areas (areas under the curves) were determined for the four isotopes in autointegration mode, and then the standard curves of the four isotopes were drawn. Quality control was made by replicate determinations of standard xenon gas. Samples of each xenon isotope were measured three times, and the mean concentration was regarded as the accurate concentration of the isotope within the chamber. The estimated concentration of xenon was the end concentration we expected within the chamber. The measured concentration was the accurate concentration of xenon measured by gas chromatography/mass spectrometer. The two concentrations were then compared to verify whether the concentration of xenon within the chamber was what we expected or not.

Definition of Loss of Righting Reflex

After each xenon concentration increment in xenon experiments, with the concentration at constant maintenance for 15 min, the chamber was gently rotated to place the mice on their backs, and the righting response was observed for 10 s. Loss of righting reflex was defined as any mouse that could not roll over during the observation period.[12] For each mouse, its loss of righting reflex ED50 was calculated by averaging successful loss of righting reflex and previous concentration of xenon. The definition was the same in the isoflurane experiment. Mouse rolling was also videoed and recorded with an iPad (Apple, Inc., USA). Any doubtful judgment during the tests was rejudged and confirmed by a second blinded experimenter by watching the video after experiments.

Determination of Loss of Righting Reflex for Mice to Isoflurane

After xenon experiments, the mice were housed for 4 days. All 80 mice were then used to determine loss of righting reflex of isoflurane. Determination of isoflurane loss of righting reflex was as the same as with xenon. The groups of mice were not changed. A group of 20 mice was tested each day. Mice were equilibrated with 0.50% isoflurane for 15 min, and then loss of righting reflex was tested. Concentration of isoflurane was increased by 0.02% until successful loss of righting reflex was observed. After experiments, loss of righting reflex ED50 for each mouse to isoflurane was calculated, and then loss of righting reflex ED50 data of the four groups were merged.

Calculation of Loss of Righting Reflex ED50 of Xenon Isotopes

We first calculated the fraction of any xenon isotope attributable to 0.50% isoflurane according to the method described by Whitehurst *et al.*[10] Because the loss of righting reflex ED50 for mice to isoflurane was 0.64%, the fraction of loss of righting reflex ED50 of xenon attributable to the constant 0.50% isoflurane maintained during the xenon studies was calculated as 0.50/0.64 = 0.78, leaving 1 to 0.78 = 0.22 loss of righting reflex ED50 fraction attributable to the xenon

isotope. The four values of xenon-bracketing loss of righting reflex ED50 were divided by the 0.22 loss of righting reflex ED50 fraction attributable to xenon, yielding the values of loss of righting reflex ED50 of the four isotopes.

Quantum Chemical Calculation of Exact Polarizability

Quantum chemical calculation of the exact polarizability of each xenon isotope was performed by using Gaussian 09 software (version D.01, Gaussian Inc., USA). The exact polarizability of each xenon isotope was optimized by b31yp/3-21G and the density functional theory method.

Statistical Analyses

The sample size in each experiment was determined based on the sample size used by Miller *et al.*[9] in their study. A larger number of mice were enrolled in this study to allow for possible incomplete data collection. GraphPad Prism software (version 6.07 for Windows, GraphPad Software Inc., USA) was used for statistical analyses. The dose-response curve was fitted by sigmoidal dose-response model as a four-parameter logistic in nonlinear regression. The nonlinear regression was used according to the equation

$$Y = Y_{min} + \left(Y_{max} - Y_{min}\right) \Big/ \left[1 + 10^{\log(ED50 - X) \times H}\right]$$

where Y is the percentage of the population showing loss of righting reflex; Y_{min} and Y_{max} are the minimal and maximal values of Y, respectively; ED50 is the averaging successful loss of righting reflex and the previous concentration; X is the logarithmic isotope dose; and H is the Hill slope constant.

Comparison of loss of righting reflex ED50 values among groups was performed with one-way ANOVA, and multiple comparisons among different groups were performed using *post hoc* tests (Bonferroni test). Data were expressed as mean ± SD. A *P* value less than 0.05 (two-tailed) was considered to be statistically significant.

Results

Anesthetic Potencies of Xenon Isotopes with 0.50% Isoflurane

There were no missing data during the experiments. After the chamber was opened, all mice invariably revived rapidly.

Dose-response curves of the four xenon isotopes with a constant 0.50% isoflurane were plotted (fig. 1). Dose-response curves of xenon isotopes with nuclear spin (^{129}Xe and ^{131}Xe) separated from those without (^{132}Xe and ^{134}Xe). One-way ANOVA analysis showed $F_{3,76}$ = 15.96 (P < 0.0001) for isotope types. The values of loss of righting reflex ED50 of the four isotopes, combined with 0.50% isoflurane, were 15 ± 4% (95% CI, 15 to 17%), 16 ± 5% (95% CI, 14 to 16%), 22 ± 5% (95% CI, 21 to 22%), and 23 ± 7% (95% CI, 22 to 24%) for ^{132}Xe, ^{134}Xe, ^{131}Xe, and ^{129}Xe, respectively. The ED50 values were then compared by a Bonferroni multiple comparisons test. The comparisons showed that, combined with 0.50% isoflurane, the values

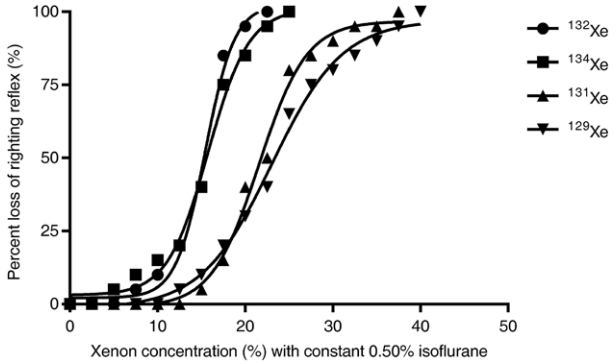

Fig. 1. The dose-response curves for four xenon isotopes with a constant concentration of 0.50% isoflurane. Best-fit sigmoidal dose-response curves are shown. The *abscissa* represents the concentrations of each isotope. Each *point* represents number of mice with loss of righting reflex under the corresponding concentration of each isotope combined with constant 0.50% isoflurane. The curves of xenon 132 (^{132}Xe) and xenon 134 (^{134}Xe) are separated from those of xenon 131 (^{131}Xe) and xenon 129 (^{129}Xe), showing that, combined with constant 0.50% isoflurane, the anesthetic potencies of ^{131}Xe and ^{129}Xe are lower than those of ^{132}Xe and ^{134}Xe (n = 20 mice per group).

of loss of righting reflex ED50 of ^{132}Xe and ^{134}Xe were comparable (P = 0.9993) with the lowest values. Loss of righting reflex ED50 of ^{131}Xe was significantly higher than ^{132}Xe (P < 0.0001) but significantly lower than ^{129}Xe (P = 0.004). Loss of righting reflex ED50 of ^{129}Xe was significantly higher than ^{132}Xe (P < 0.0001; fig. 2). Because the higher the loss of righting reflex ED50 the lower the anesthetic potency, these results showed that, combined with 0.50% isoflurane, xenon isotopes with nuclear spin had lower anesthetic potencies than those without.

Anesthetic Potencies of Xenon Isotopes Alone

In order to determine the anesthetic potencies of xenon isotopes without isoflurane, we determined isoflurane loss of righting reflex ED50 in the same mice. Our result showed that the loss of righting reflex ED50 for the same mice to isoflurane was 0.64 ± 0.01% (95% CI, 0.64 to 0.65%; fig. 3). Using 0.64% as the loss of righting reflex ED50 for the mice to isoflurane, we calculated the fraction of loss of righting reflex ED50 of any xenon isotope attributable to the constant 0.50% isoflurane, and then the fractions yielded the values of loss of righting reflex ED50 of the four isotopes alone according to the method described by Whitehurst *et al.*[10] We found that the values of loss of righting reflex ED50 of ^{132}Xe, ^{134}Xe, ^{131}Xe, and ^{129}Xe were 71 ± 4% (95% CI, 70 to 72%), 72 ± 5% (95% CI, 71 to 73%), 99 ± 5% (95% CI, 96 to 99%), and 105 ± 7% (95% CI, 104 to 106%), respectively. Again, the values of loss of righting reflex ED50 of ^{132}Xe and ^{134}Xe were comparable (P = 0.42). ^{129}Xe loss of righting reflex ED50 was significantly higher than ^{132}Xe (P < 0.0001). ^{131}Xe loss of righting reflex ED50 was

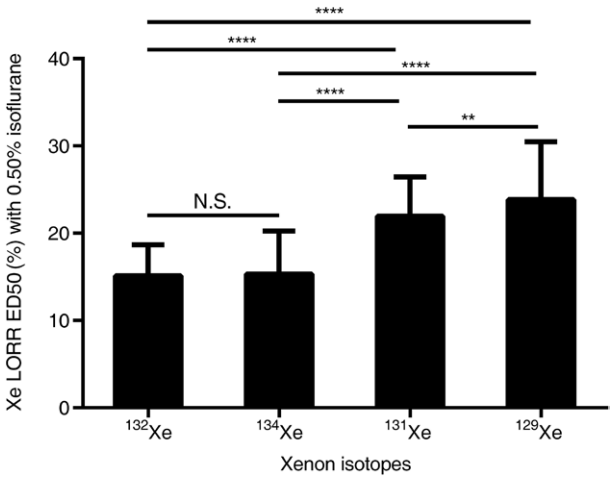

Fig. 2. The values of ED50 of loss of righting reflex for mice to four xenon isotopes with a constant concentration of 0.50% isoflurane. The values of loss of righting reflex (LORR) ED50 of xenon 132 (^{132}Xe) and xenon 134 (^{134}Xe) are comparable. Loss of righting reflex ED50 of xenon 131 (^{131}Xe) is significantly higher than ^{132}Xe and ^{134}Xe but significantly lower than xenon 129 (^{129}Xe). Loss of righting reflex ED50 of ^{129}Xe is significantly higher than ^{132}Xe and ^{134}Xe. Data are shown as mean (SD), n = 20 mice per group. $^{**}P < 0.001$; $^{****}P < 0.0001$; N.S. = not significantly different (one-way ANOVA followed by the Bonferroni correction as a *post hoc* test).

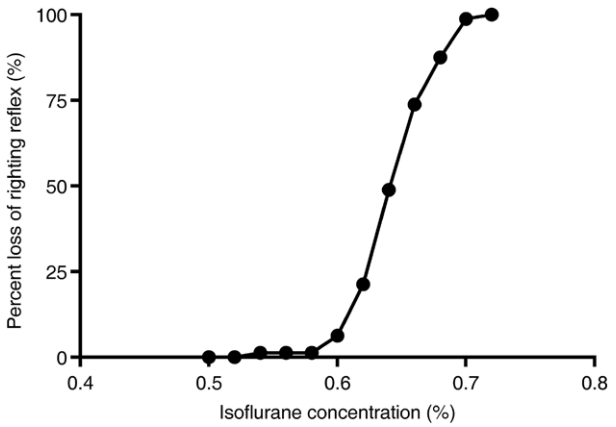

Fig. 3. The dose-response curve for mice to isoflurane. The best-fit sigmoidal dose-response curve is shown. The *abscissa* represents for isoflurane concentrations. Each *point* represents the percent of sum number of mice with loss of righting reflex under the corresponding concentration of isoflurane (n = 80 mice).

significantly higher than ^{132}Xe ($P < 0.0001$) but significantly lower than ^{129}Xe ($P = 0.003$). The values of loss of righting reflex ED50 of the four isotopes are shown in figure 4.

Xenon Concentrations

At the end of any xenon experiment, a gas sample was drawn from the chamber, and the concentration of xenon was detected with gas chromatography/mass spectrometer. We found that the detected concentrations of the xenon isotopes were respectively the same as expected concentrations within the chamber.

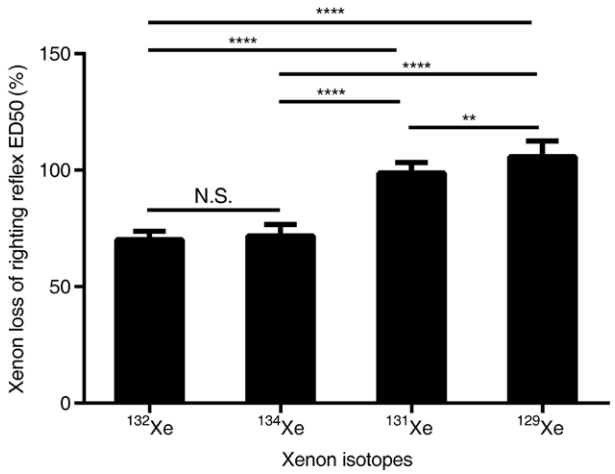

Fig. 4. The values of loss of righting reflex ED50 for mice to four xenon isotopes alone. The data of loss of righting reflex were calculated by the fractions of loss of righting reflex ED50 of xenon isotopes attributable to constant 0.50% isoflurane with isoflurane ED50 as 0.64%. The values of loss of righting reflex ED50 of xenon 132 (^{132}Xe) and xenon 134 (^{134}Xe) are identical. Loss of righting reflex ED50 of xenon 129 (^{129}Xe) is significantly higher than ^{132}Xe and ^{134}Xe. Loss of righting reflex ED50 of xenon 131 (^{131}Xe) is significantly higher than ^{132}Xe and ^{134}Xe but significantly lower than ^{129}Xe. Data are shown as mean (SD), n = 20 mice per group. $^{**}P < 0.001$; $^{****}P < 0.0001$; N.S. = not significantly different (one-way ANOVA followed by the Bonferroni correction as a *post hoc* test).

Exact Polarizabilities of Xenon Isotopes

We calculated the values of exact polarizabilities for all four isotopes using a density functional theory approach. The results of our quantum chemical calculations showed that all four isotopes had the same value of exact polarizability of 3.60 Å^3.

Discussion

In this paper, we present that xenon isotopes with nuclear spin (^{129}Xe and ^{131}Xe) are less potent to prevent consciousness than those without (^{132}Xe and ^{134}Xe). Because they are chemically the same, it is their physical properties that might contribute to the differences of the anesthetic potencies. There are two main physical properties of xenon isotopes: atomic mass and nuclear spin. The difference of atomic mass between ^{129}Xe and ^{132}Xe is the mass of three neutrons, but the ^{129}Xe loss of righting reflex ED50 is 149% of that of ^{132}Xe. The difference of atomic mass between ^{134}Xe and ^{132}Xe is the mass of two neutrons, and their values of loss of righting reflex ED50 are comparable. Therefore, the differences of the values of loss of righting reflex ED50 among the four xenon isotopes cannot be explained by the differences of atomic mass, leaving nuclear spin the only factor to affect xenon isotopes to prevent consciousness.

Xenon, the simplest general anesthetic, is a monoatomic noble gas. *N*-methyl-D-aspartate receptor as the target of xenon has been proposed.[5,13] However, xenon follows the

Meyer-Overton correlation, and thus binds in many proteins and nonpolar sites. Targeting of *N*-methyl-D-aspartate receptor cannot explain the huge differences of the anesthetic potencies between xenon isotopes with nuclear spin and those without because they are chemically the same. Although we do not know how microscopic nuclear spin can affect the macroscopic brain so much, we can anticipate that the huge difference of anesthetic potency between ^{129}Xe and ^{132}Xe should make the two isotopes regarded as two different anesthetics, and thus ^{129}Xe and ^{132}Xe may be tools to check any hypothesis of mechanism of anesthetic action of general anesthetics.

A unitary correlation between anesthetic polarizability and anesthetic potency has been proposed.[14] Xenon has a high polarizability. There is thus a possibility that different polarizabilities among xenon isotopes might account for their differences of anesthetic potencies. However, this is not the case, as our quantum calculations show that the four isotopes have an identical exact polarizability.

A correlation between potency of anesthetics and their solubility in hydrophobic pockets of proteins, binding there by van der Waals London forces, has been proven.[15,16] The interactions between inhaled anesthetics and proteins, including the concepts of van der Waals London forces, have been reviewed by Eckenhoff and Johansson.[17] For van der Waals London forces, in brief, the attractive van der Waals forces include dipole–dipole, induced dipole–dipole, and London interactions. Dipole–dipole interactions result from attraction of unlike partial charges on molecules and groups, most of which have a permanent dipole moment. Induced dipole–dipole interactions result from the distortion of an atom's electron cloud (polarizability) in the presence of a strong dipole moment. London force, also called dispersion force, a weak van der Waals force, is the case where momentarily opposed dipole moments (transient dipole moments) are formed due to normal fluctuations in the charge distribution when the electron cloud of one atom influences that of one nearby.[17] Xenon binding to myoglobin[16] must occur entirely through van der Waals interactions, being limited to induced dipole–dipole and London-type interactions.[17] If the conclusion is true, van der Waals London forces cannot account for the difference in anesthetic potency among the four xenon isotopes in this study. It is well known that all molecules experience temporary fluctuating dipoles and that molecules having permanent dipoles will have boiling points rather higher than those only having temporary dipoles. To our knowledge, no difference in boiling point among xenon isotopes has been reported. Xenon isotopes may thus have similar dipole–dipole interactions if xenon has permanent dipoles. The strength of dispersion forces (London forces) varies considerably with the size of the molecule and its shape. The four xenon isotopes have negligible differences in mass and all are spheres in shape. Therefore, the four isotopes may have identical London forces. The last kind of interaction arising from van der Waals forces is attributed to polarizability. A striking correlation between van der Waals force and rare gas (including xenon) polarizability has been proven,[18] and there is a relationship between atomic polarizability and properties such as volume, radius, softness, hardness, and potential electronegativity.[19] Because the four xenon isotopes have an identical exact polarizability, their induced dipole–dipole interactions should also be identical. Taken together, van der Waals forces cannot give rise to the difference in anesthetic potency among the xenon isotopes.

As the four isotopes have negligible difference in atomic mass and have no difference in outer electron shell, the explanation of the difference in anesthetic potency among them may be in the atomic nucleus. Nuclear spin is a quantum feature of the atomic nucleus. Quantum calculations[20,21] and experimental evidence[22,23] have shown that atoms with nuclear spin of 1/2 are more capable of forming quantum entanglement than those with other types of nuclear spins. ^{129}Xe (with a nuclear spin of 1/2) may thus be more capable of entangling with the other particles than the other xenon isotopes. Entangled particles send information at a distance, and this may be the case in conscious processing. Fisher[20] theoretically presumed that the element hosting the site for quantum consciousness—a putative "neural qubit"—must have nuclear spin of 1/2 because 1/2 spins are unlikely to be decohered. This presumption implies that the lower anesthetic potency of ^{129}Xe may be due to it participating in and somehow enhancing conscious processing, and therefore partially antagonizing its own anesthetic potency. Fisher[20] suggested nuclear spin was conveyed by adenosine triphosphate phosphorylation. Craddock *et al.*[24] proposed quantum memory is encoded by synaptically activated calcium-calmodulin kinase II phosphorylation on microtubule lattices. The relation between nuclear spin and quantum processes in electron clouds as defined by Meyer-Overton is unclear, and deserves further study, as does the role of nuclear spin in mental states in general. Our results suggest that the quantum property of nuclear spin in the monoatomic anesthetic xenon promotes conscious processes at the xenon site of action, consistent with theories proposing quantum mechanisms in consciousness.

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Competing Interests

The authors declare no competing interests.

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