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Noble Gases in Pure Lipid Membranes

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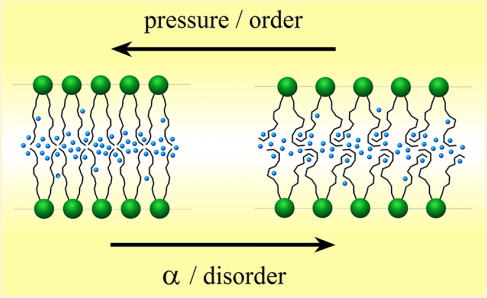
ABSTRACT: The mechanism of how a noble gas modifies the excitability of nerve cells and how such excitability can be recovered under hyperbaric pressure remains unclear. Here we present a calorimetric study where the melting point depression of pure lipid membranes induced by noble gases and its recovery with a hydrostatic pressure is addressed. A correlation is found between the electric polarizability (α) of these gases and their effect on the melting transition of the membranes. These results concur with other findings to support the idea that general anesthesia only depends on the ability of a certain atom or molecule to increase the general disorder of the membrane.



INTRODUCTION

For well over a century, general anesthesia has been one of the great unfinished issues of neuropharmacology.[1] Nowadays, one can find an overwhelming variety of different substances that induce anesthesia, where the most common action sites have been directed to either lipids or proteins. Authors pursue different theories: anesthetics act within the hydrophobic interior of the lipid bilayer itself,[2] at the interface between the lipid and the aqueous phase,[3] at the water/protein interface,[4] between hydrophobic α-helices of crucial excitable proteins,[5] or at the lipid/protein interface.[6]

Is there a relevant action site for the anesthetic phenomenon? The main key of this problem emerges from the fact that general anesthesia is pressure-dependent. Early indications of the pressure reversal effect were shown in tadpoles swimming,[7] where the anesthetic effect of ethanol and ethyl carbamate was reversed upon application of a hydrostatic pressure (200−300 atm). In addition, experimental work on pressure reversal has been extended to newts, mice, and marine organisms,[8−10] where the pressure reversal for a large number of both liquid and gaseous anesthetics was convincingly demonstrated.

Irrespective of which theory is the correct one, it has been proved indisputably that, whatever the action site is, it is hydrophobic. This assumption is primarily based on the rule of thumb independently observed by Meyer[11] and Overton[12] at the turn of the last century, which states that the potency of general anesthetics correlates strongly with their solubility in olive oil (the Meyer−Overton rule). Indeed, no other rule based on physicochemical and structural parameters has been as useful in predicting anesthetic potency in the prevailing pharmacology. It is important to mention that the first anesthetic−protein correlation was observed with the functional inhibition of the lipid-free soluble protein firefly luciferase,[13] and although probably unrelated to anesthesia, it was used to support the idea that hydrophobic sites can also be modeled by a protein. Nonetheless, this protein does not display pressure reversal.[14]

Furthermore, the classical protein model for the nerve pulse propagation and its relation to anesthesia has been challenged by a thermodynamic model proposed by Heimburg and Jackson,[15] which is in accordance with the Meyer−Overton rule and with a number of other unexplained observations present during the action potential propagation.[16,17]

In spite of the fact that the current fashion of the biological mechanisms makes us resort to proteins, we must not neglect that anesthetics produce the melting point depression phenomenon in pure lipid systems.[18,19] Besides, it is also well recognized that gaseous, alcohol, steroid, amine, and barbiturate anesthetics dilate, fluidize, and disorder lipid bilayers[2] and the increase of hydrostatic pressure induces a shift in the melting transition to higher temperatures.[20,21] Indeed, it is shown that, while anesthetics lower the melting point, hydrostatic pressure recovers it.[22,23] These factors rephrase the Meyer−Overton correlation as: the critical anesthetic dose ED_{50} (where 50% of individuals lose consciousness) is proportional to their ability to lower phase transitions. As a consequence, and based on the model of Heimburg and Jackson, nerve membranes are less excitable.[17]

Although noble gases have apparently minimal capacities to interact with a putative action site, xenon is clinically used as an anesthetic.[24] Further, krypton and argon show anesthetic-like effects at hyperbaric pressures, while, in contrast, neon and helium, do not cause anesthesia.[25−27] Conspicuously, even nitrogen is known to induce narcosis at hyperbaric pressures.[28] At present, specific action sites in proteins are not well identified neither for noble gases nor for N_2. However, some studies propose an inhibitory action in hydrophobic sites or pockets within ion channels such as the *N*-methyl-D-aspartate

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(NMDA)[29,30] and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors,[31,32] while having little or no effect on $GABA_A$ receptors.[29,33] Other proteins have been used to speculate about such an effect.[34,35] Irrespective of any protein, this perception hints to protein structural changes caused by anesthetics. Although it has been justified through dislocation/dissociation of the anesthetic molecule from their expected binding sites,[36] hydrostatic pressure could hardly provide structural reversibility.

Recently, Yamamoto et al.[37] performed molecular dynamics simulations (MDS) to study the diffusive nature of xenon within lipid bilayers. They reported a decrease in the orientational order of the lipid tails, an increase in the area and volume per lipid molecule, and an increase in the diffusivity of lipid molecules, followed by pressure reversal evidence of such a disordering effect.

The elegant simplicity of the noble gases arises from the fact that all of these elements have outer shells completely filled with electrons, they are spherically symmetric, and, as a consequence, they are uncharged and do not have permanent dipole moments. This peculiarity makes them nonreactive to form covalent bonds with other elements. Such noble characteristics magnify the problem of explaining how rare gases produce anesthesia in a specific and lasting bond according to the protein receptor hypothesis. Thus, the role of noble gases in anesthesia may give us some hints toward a suitable general anesthetic mechanism. Equally essential, any attempt to define such a molecular mechanism must also explain pressure reversal.

The work we report in this article follows the steps of the MDS results obtained by Yamamoto et al.[37] However, we go further and present, for the first time, a calorimetric study of the melting point depression phenomenon in pure lipid membranes induced not only by xenon but by three other noble gases (He, Ar, and Kr). Moreover, we also study the pressure reversal effect of the melting point depression obtained with xenon.

METHODS

Liposome Preparation. 1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC, Avanti Polar Lipids, Birmingham, AL) was handled without further purifcation. An aqueous buffer was used to hydrate the lipids above the their melting transition (Milli-Q-water, 10 mM HEPES, pH 7, 50 °C). The dispersion was softly vortexed for 30−60 min at 50 °C. This procedure yields multilamellar vesicles (LMVs or MLVs). Small unilamellar vesicles (SUVs) were prepared from the MLV dispersions by sonicating for 30 min at 50 °C in a water-bath ultrasonicator (60 W). The resulting SUV suspension was subjected to 2.5 cooling−heating cycles from 50 to 25 °C in order to achieve a stable liposome size (10−15 nm) for the experimental requirements. Liposome size was measured with a Zetasizer (Nano Zs, Malvern).

Pressurizing Process with Noble Gases. A self-built high-pressure system was used to expose the liposome suspension to the noble gases (He, Ar, Kr, and Xe); see Figure 1. The liposome sample (1) is deposited into the aluminum chamber (7), which is sealed by a thick lid of the same material. The container of the desired noble gas is connected to the introduction valve (2). Previously to the pressurizing process, air inside is replaced by ventilation of the desired noble gas using the purge valve (3). After a few seconds of ventilation, this valve is completely closed. With the purpose of achieving a proper thermodynamic stability of the membranes, at least 10 min of thermalization is required. The temperature of the samples is controlled by a water recirculating system (PolyScience) connected to the aluminum chamber that contains inner channels where water circulates (6). It is important to ensure that the initial position of the plunger (5) is fully inserted. Once the desired gas is occupying the sample compartment and the thermalization is achieved, the plunger (5) is withdrawn to its maximum position for charging the desired gas. This allows us to reduce the gas consumption as well as acquire higher pressures than those provided by the gas tank. The pressurizing system was designed to attain high pressures, allowing us to increase around 10 times the initial pressure of the chamber. The gas introduction valve (2) is closed, and the plunger starts to be introduced to increase the pressure up to the required value, which is monitored by a gauge pressure (4). When we reach the desired pressure, the exposure time begins. It is important to note that all the pressurizing process parameters (exposure time, temperature, and gas pressure) vary according to the experiment. All assays were carried out at a constant volume of liposome suspension (1.2 mL). Once the exposure time is completed, the gas purge valve (3) is used to slowly release the gas, avoiding any unwanted expulsion of the sample. Finally, once the gas exits the chamber, the liposome suspension can be withdrawn to be used in the calorimetric experiments. Henry's law helps us to understand how the gases are incorporated into the aqueous suspension.[38,39] This law states that, at constant temperature, the solubility of a certain gas in a liquid is directly proportional to the pressure of the gas above the liquid.

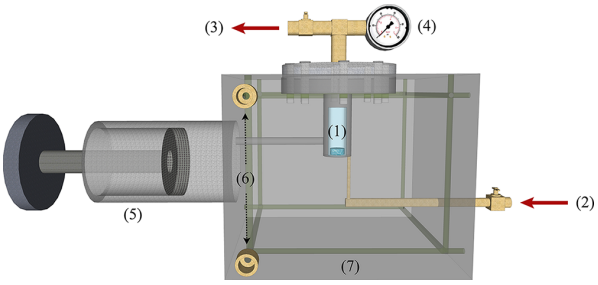

Figure 1. Schematic drawing of the high-pressure experimental setup. (1) Liposome suspension; (2) Gas introduction valve; (3) Gas purge valve; (4) Gauge pressure; (5) Plunger; (6) Inflow/outflow water recirculating system; (7) Solid aluminum chamber.

Calorimetric Analysis. Heat capacity profiles were recorded at a lipid concentration of 4 mM, with a heating rate of 1 °C/min. Before the samples were loaded into precooled DSC cuvettes, the samples were degassed at low pressure (635 mmHg) for 10 min at 25 °C. Note that the heat capacity is measured at constant pressure (3 atm) with the exception of the pressure-reversal study. The calorimeter (Microcalorimeter, NanoDSC, TA Instruments) was interfaced to a PC, and data were analyzed using the software provided with the instrument. Just before starting the calorimetric scan, the samples were equilibrated for 8 min at 25 °C. Three heating scans from 25 to 50 °C were realized for each sample. Each experiment was performed two times using different sample preparations. Namely, the calorimetric scans were reproducible (scan to scan and sample to sample), indicating that, in our experimental protocol, the final liposome suspension reached equilibrium.

RESULTS AND DISCUSSION

Since choline phospholipids are the most abundant species in plasma membranes,[40] we prepared vesicles (SUVs) as previously mentioned.

In order to explore the diffusivity of noble gases in the liposome–water system, a careful characterization study was previously conducted. Figure 2 shows the absolute value of the melting temperature shift ($|\Delta T_m|$) of the xenon-doped liposomes as a function of the exposure time (circles), at 4 atm of Xe and at 30 °C. From these results, it is observed that 2 h of maintaining the liposomes under xenon pressure represents the minimum exposure time to allow this gas to diffuse into the liposome membranes and produce its maximum effect. An analogous correlation is observed for xenon pressures (triangles), with pressurizing parameters of 2 h and 30 °C. From the latter, the saturation point (~3 atm) represents the maximum capacity of the liposome membrane to contain xenon atoms and induce the greatest effect on the melting point. Just as for Xe, a similar tendency but lower saturation points are found for He, Ar, and Kr (data not shown here). No dependence is found with the thermodynamic state of the membrane, i.e., temperature below (gel phase) or above (liquid phase) T_m during the pressurizing process, and the xenon effect in membranes. Gas solubility in water is given by the Henry's constant (k_H) which in turn is thermal dependent.[38] Henry's law can be used to get an approximation of the gas concentration in the aqueous medium as a function of the applied pressure. We show this procedure for xenon parameters, but a similar approximation can be outlined for other gases, using their corresponding k_H at the temperature of the experiment.

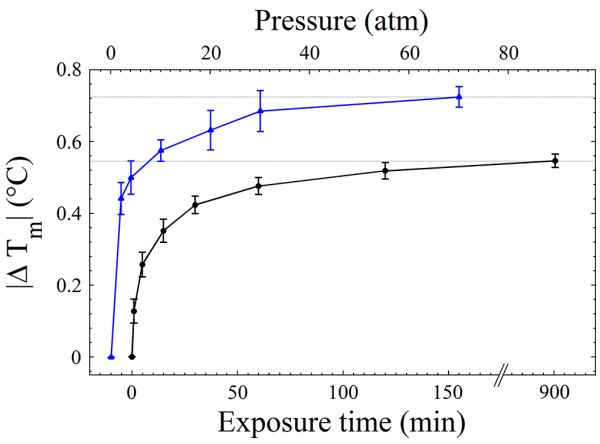

Figure 2. Characterization study of the xenon diffusivity. Melting temperature shift $|\Delta T_m|$ as a function of xenon exposure time (circles) and pressure (triangles). Since ΔT_m is always negative (the final temperature is always lower than the initial one), we plot its absolute number to illustrate the saturation of the shift at high exposure times and pressures. The control melting temperature for DPPC was 41.815 ± 0.011 °C, measured at 3 atm.

The k_H of xenon is about 1.4×10^{-4} $mol_{gas}/(atm \cdot mol_{soln})$ at 30 °C.[38] From the molecular mass of water (~18.015 g/mol) and its density (~995.678 g/L) at 30 °C,[41] a water molarity of ~55.269 mol/L is obtained. Relating these parameters with Henry's law, and using 1 atm of xenon, one can estimate a gas molarity of ~7.738×10^{-3} mol_{gas}/L. Due to the linearity of this law, a general relation between gas molarity (M_{Xe}) and pressure (P_{Xe}) can be established at 30 °C: $M_{Xe} \approx 7.738 \times 10^{-3}$ $mol_{gas}/(atm \cdot L) \cdot P_{Xe}$.

Pressure reversal evidence is presented in Figure 3. It shows the calorimetric profile of xenon-doped liposomes (4 atm, 2 h, 30 °C) measured at several hydrostatic pressures (1, 3, and 6 atm) applied by the calorimeter. Helium-doped liposomes (same pressurizing conditions) were used to show that pressure per se does not affect the results. The inset clearly illustrates that the greater the hydrostatic pressure applied over the system, the lower the $|\Delta T_m|$. It is important to mention that the maximum hydrostatic pressure attained by our calorimeter is 6 atm; thus, only a partial but decisive pressure reversal effect is observed. However, it is clear that a greater hydrostatic pressure would be able to completely recover the T_m to normal conditions.

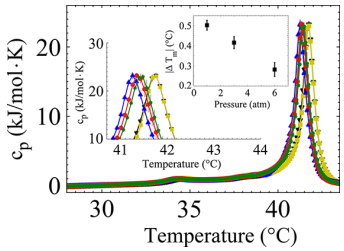

Figure 3. Pressure reversal study: calorimetric profiles at several hydrostatic pressures (scanning pressure). Triangles down are for control liposomes at 1 atm, squares for He-doped liposomes at 1 atm, and triangles, circles, and stars for Xe-doped liposomes at 1, 3, and 6 atm, respectively. Liposomes were doped with both gases at the same pressurizing conditions (4 atm, 2 h, 30 °C). The inset shows the melting temperature shift $|\Delta T_m|$ as a function of the hydrostatic pressure. Note that $|\Delta T_m| = 0$ would represent a complete recovery of the xenon effect due to pressure and such an effect seems to be linear.[15]

Physiologically, the most noteworthy effect of pressure is the hyperexcitability that occurred by trembling of the extremities followed by convulsions, while a further increase leads to paralysis and death. These antagonistic effects of hyperbaric pressure (excitability) and the inert gases (depressivity) have been elucidated by a nonspecific model where the lipid structure of nerve membranes is modified. This model is known as the critical volume hypothesis:[9,42] a lipid bilayer expands due to the anesthetics dissolved therein, while pressure causes a volume recovery of the same. In fact, hyperexcitability, modeled as an excessive compression of the membrane, is still not well understood by the current models of neuroscience, although it is seamlessly in accordance with the soliton model for nerve impulse propagation.[16] Suitable mixtures of "expanding" and "compressing" gases may allow high pressures to be more tolerable in mammals. This mere theory has been empirically considered to solve the physiological adversities shown for divers.[43,44]

Inasmuch as noble and some diatomic gases are uncharged and nonpolar, there are no Coulombic components involved in binding. Nonetheless, two imperative components of the van der Waals binding energy remain: the charge-induced dipole term (Debye energy) and the induced dipole–induced dipole term (London dispersion energy). The electric-dipole polarizability (α) is a physical property closely related to these dispersion energies and stands for a measure of the electron

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cloud distortion of the interacting molecules. The larger the atom/molecule (i.e., the larger the electronic cloud), the greater the α, and hence its hydrophobicity. Therefore, the greater the α of an anesthetic, the greater its tendency to reach the hydrophobic core of lipid membranes, which may perturb the lipid tail structure.

Figure 4 shows the melting temperature shift produced by noble gases and their respective α. Neon, which its effect can

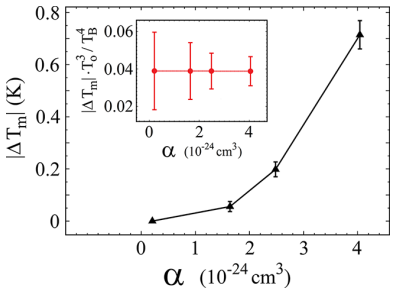

Figure 4. Polarizability of the noble gases. Melting temperature shift as a function of the electric-dipole polarizability of noble gases. The inset shows a dimensionless collapse of the same effect with the boiling points (T_B) of the respective gas and the experiment temperature (T_0). T_B, as some other properties of these gases, is directly related to the van der Waals interactions where alpha is implied, whereby the obtained collapse shows that α may be considered as a signature in the effect produced by noble gases. The gas polarizabilities were taken from ref 45.

certainly be considered between helium and argon, was not implemented in this work. All gases were employed under the same conditions, looking for their maximum effects: 100 atm of pressure for 2 h at 70 °C (T_0). The inset in Figure 4 illustrates a dimensionless collapse to the same value (~0.04) of this shift using the boiling points for each gas (T_B) and the experiment temperature (T_0). T_B is directly related to the van der Waals interactions where α is the key parameter, whereby the obtained collapse shows that α may be considered as a signature in the effect produced by noble gases.

From the smallest electron shell of helium up to the largest one of xenon, a meaningful correlation occurs: the higher the α value, the larger the shift of T_m to lower temperatures. Since temperature is a manifestation of kinetic energy and cohesion of potential energy, the interplay between these two forms of energy is responsible for the physical properties of matter.[46] Thus, if the cohesion of a given system is decreased, less temperature is needed to melt it. This is clearer to understand if we recall that there is always a trade-off between enthalpic and entropic terms as expressed in the free-energy equation: $G = H - TS$.[47] When a noble atom diffuses into the membrane, H becomes less negative (i.e., the cohesive potential energy wall between lipids decreases); hence, S augments as the system becomes increasingly disordered. Such increment of enthalpy, due to an intruder noble gas, could be explained using the triple-dipole Axilrod–Teller term in the interaction potential.[48,49] This term is positive for an acute triangular arrangement of atoms and negative for near linear geometries. Note that most of the time the third-body interaction is positive because thermal energy increases the probability of acute triangle configurations. Two lipid tails in a membrane are linked by a van der Waals interaction (the effective cohesion of the whole system is given by the sum of these pairwise interactions). Now, a noble atom approaches these tails and interacts with them as a third body, perturbing the lipid–lipid interaction with a positive contribution that is proportional to α and scales as r^{-9}.[48] In rare gases, this contribution is very small and does not affect any measurable property, except when atoms form a crystal.[48] This is why in the case of a membrane (a lipid crystal-like) the third-body effect is noticeable, reducing the cohesion and therefore T_m. In summary, seen as a cause-effect phenomenon, the following course of events occurs: a noble gas enters in the membrane, reduces the cohesion (via the positive triple-dipole term), enthalpy is increased, entropy also increases, and the melting temperature drops. This suggests a clear connection between α and the structural changes exerted by noble gases in lipid membranes. The effect is schematically depicted in Figure 5.

While some molecular dynamics studies report a higher affinity of xenon at the hydrophobic core of the membrane,[37] other experimental studies suggest that xenon–membrane interaction is directed toward the amphiphilic region of lipids.[50] However, regardless which is the precise region of action at the lipid membrane, membrane disorder caused by noble gases is an inexorable fact.

CONCLUSION

A calorimetric study of pure lipid membranes doped with noble gases has been addressed. We found that the electric polarizability (α) of these gases is correlated with the melting point depression of pure lipid membranes. We speculate that this depression could be related to a third-body interaction

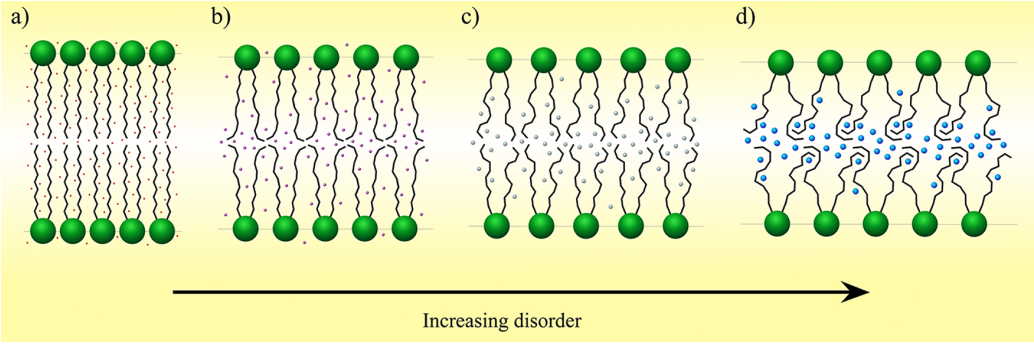

Figure 5. Schematic representation of a membrane section where the structural changes produced by (a) He, (b) Ar, (c) Kr, and (d) Xe are depicted.

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potential. Our experimental evidence confirms that the hydrostatic pressure recovers the structural changes induced by noble gases, which is in agreement with other findings supporting the idea that anesthesia does not need a specific binding site in proteins. Physical variables of lipid membranes, such as lipid order, lateral area, and volume, can be gradually altered with the inclusion of inert atoms which share a unique physical variable in common: their size or polarizability. Additional molecular features are needed to elucidate the lipid disorder created by other more complex anesthetic species.

In neurons, some crucial proteins related with their natural activity are strongly dependent on the lipid fluidity of the surroundings. Work in this direction has demonstrated that halothane at physiological concentrations produces a pronounced redistribution of lipids between domains of different lipid types.[51] Therefore, it is not entirely rejectable that anesthetics, at least noble gases, alter the membrane structure at the lipid neighborhood of these proteins up to a point that their normal functions are disturbed. A rigorous study of such a hypothesis is worth being pursued in order to remove the need of a very large number of protein receptors for hundreds of different anesthetic species.

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Notes

The authors declare no competing financial interest.

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