Pharmacology & Therapeutics 160 (2016) 44–64

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: M. Belvisi

The diverse biological properties of the chemically inert noble gases

David A. Winkler [a,b,c,d,*], Aaron Thornton [a], Géraldine Farjot [e], Ira Katz [e,f]

[a] CSIRO Manufacturing, Bag 10 Clayton South MDC 3169, Australia
[b] Monash Institute of Pharmaceutical Sciences, 392 Royal Parade, Parkville 3052, Australia
[c] Latrobe Institute for Molecular Science, Science Dr, Bundoora 3083, Australia
[d] School of Chemical and Physical Sciences, Flinders University, Bedford Park 5042, Australia
[e] Medical R&D, Air Liquide Santé International, Centre de Recherche Paris-Saclay, 1, Chemin de la porte des Loges, BP 126 Les loges en Josas, 78354 Jouy en Josas Cédex, France
[f] Department of Mechanical Engineering, Lafayette College, Easton, PA 18042, USA

ARTICLE INFO

Available online 16 February 2016

Keywords:
Noble gases
Chemically inert
Clinical applications
In vitro and *in vivo* studies
Drug delivery

ABSTRACT

The noble gases represent an intriguing scientific paradox. They are extremely inert chemically but display a remarkable spectrum of clinically useful biological properties. Despite a relative paucity of knowledge of their mechanisms of action, some of the noble gases have been used successfully in the clinic. Studies with xenon have suggested that the noble gases as a class may exhibit valuable biological properties such as anaesthesia; amelioration of ischemic damage; tissue protection prior to transplantation; analgesic properties; and a potentially wide range of other clinically useful effects. Xenon has been shown to be safe in humans, and has useful pharmacokinetic properties such as rapid onset, fast wash out etc. The main limitations in wider use are that: many of the fundamental biochemical studies are still lacking; the lighter noble gases are likely to manifest their properties only under hyperbaric conditions, impractical in surgery; and administration of xenon using conventional gaseous anaesthesia equipment is inefficient, making its use very expensive. There is nonetheless a significant body of published literature on the biochemical, pharmacological, and clinical properties of noble gases but no comprehensive reviews exist that summarize their properties and the existing knowledge of their models of action at the molecular (atomic) level. This review provides such an up-to-date summary of the extensive, useful biological properties of noble gases as drugs and prospects for wider application of these atoms.

Contents

1. Introduction

The noble gases helium, neon, argon, krypton, xenon, and radon have full valence electron shells and are, consequently, extraordinarily chemically unreactive. While it is possible to carry out interesting chemistry on these atoms, generally very harsh conditions are required to do so. Paradoxically, they are far from inert biologically, although this appreciation is relatively recent and the mechanisms responsible for

Abbreviations: CNS, central nervous system; logP, log of the octanol-water partition coefficient; L1, L2, Ostwald coefficients; DMPC, 1,2-dimyristoyl-sn-glycero-3-phosphocholine; GABA, gamma aminobutyric acid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartate.

* Corresponding author at: CSIRO Manufacturing, Bag 10, Clayton South MDC 3169, Australia. Tel.: +61 3 9545 2477.
E-mail address: dave.winkler@csiro.au (D.A. Winkler).

http://dx.doi.org/10.1016/j.pharmthera.2016.02.002
0163-7258/

biological activity are generally not well understood. It is known that the heavier atoms xenon, and to a lesser extent argon and krypton, have very interesting molecular interactions with a number of important proteins involved primarily in cell signaling, although the literature on this is relatively small and the fascinating biology of these atoms is still being uncovered. Interestingly, xenon has been used in the clinic before all of the mechanisms of action have been elucidated, so there is still much to learn about how xenon and, potentially, the other noble gases interact with biology. The noble gases exhibit valuable properties such as almost ideal anaesthesia, neuroprotection, effective analgesia, and useful central nervous system (CNS) effects on memory and addiction. Xenon exhibits little or no toxicity and washes out very quickly after administration ceases, leading to rapid recovery. Similar safety and distribution profiles are anticipated for the other noble gases. Wider exploitation of these clinical benefits has largely been stalled by the need for hyperbaric administration of the lower atomic weight noble gases to patients, and the very high cost of the heavier noble gases like xenon due to its rarity. Xenon and argon also have demonstrated valuable *in vivo* capabilities to alleviate the long-term sequelae after stroke or other ischemic insults in animal models. Translation into beneficial effects in human is challenged by the difficulty in demonstrating clinical efficacy in those pathologies. Further exploration of biological properties of noble gases and improvements in their delivery systems are necessary to open up much greater use of these materials.

Given the relative dearth of preclinical biological information in the literature and the potential clinical importance of these elements as therapeutics, we review the published literature on the biological effects of noble gases, most of it occurring since 1980 (the beginning of substantial studies on the biological effects of noble gases). The review is divided into several sections. The physical properties of the noble gases are reviewed in Section 2. This provides a rational basis for understanding the types of interactions noble gases may have with protein targets. Studies of the effects of noble gases on specific molecular targets are reviewed in Section 3. Studies of the *in vivo* or *in vitro* effects of noble gases on tissues, cells, or organs are reviewed in Section 4. Possible solutions to the noble gas delivery and cost problems are discussed in Section 5. Section 6 provides a brief summary of the use of noble gases in structural biology. Section 7 discusses the important role of computational modeling methods in providing insight into the mechanisms of interaction of noble gases with proteins, and to leverage the limited experimental data on biological activity of noble gases. Section 8 provides some perspectives on the promise of noble gas therapeutics, and how some of the current limitations in delivery and mechanistic understanding can be overcome, and the final section provides conclusions.

2. Physical and physicochemical properties of noble gases

The noble gases are generated by primordial processes and radioactive decay and so occur naturally in the environment (Pepin, 1992). Helium comes from the alpha decay of heavy elements such as uranium and thorium, and argon is formed by the beta decay of potassium-40. Xenon has an unexpectedly low abundance in the atmosphere (called the missing xenon problem) (Dmochowski, 2009; Shcheka & Keppler, 2012) as it is thought to be locked in minerals inside the Earth's crust. Radon is formed by the alpha decay of radium. The primordial origin of the terrestrial signature of the noble gases is described by Shcheka in a recent Nature paper (Shcheka & Keppler, 2012). The concentrations of the noble gases in the atmosphere are 5.2 ppm for He, 18.2 ppm for Ne, 9340 ppm for Ar, 1.1 ppm for Kr and 0.09 ppm for Xe (Joyce, 2000). The high cost reflects this rarity, with 2004 prices for 1 m^3 of these gases costing $4–40 for He (extracted from natural gas rather than the air), $3–9 for Ar, $60–120 for Ne, $400–500 for Kr, and $4000–5000 for Xe (Hwang et al., 2005). The cost of xenon has been a major deterrent to its clinical use in general anaesthesia (Nakata et al., 1999; Joyce, 2000; Reyle-Hahn & Rossaint, 2000; Baskar & Hunter, 2006; Bruecken et al., 2010; Jordan & Wright, 2010).

One of the most biologically relevant properties of noble gases is their solubility in water or other biological fluids. One of the first studies of the solubilities in water, plasma, and blood were carried out by Hardewig et al. (1960). Subsequent studies investigated the solubility of noble gases in water in more detail (Bennaim, 1964). Christof and Hedleywh compared the whole blood solubilities of He with those of nitrous oxide (N_2O) and nitrogen (N_2) (Christof & Hedleywh, 1970). Weatherby and Homer published a comprehensive review of more than 150 studies of the solubilities of noble gases in biological fluids and tissues (see Table 1) (Weathersby & Homer, 1980).

Battino et al. measured the partition coefficients of the noble gases except xenon in isobutanol/water and olive oil/water systems (Battino et al., 1971). The partitioning into the organic phase increased from He to Ar, consistent with increasing atomic number and lipophilicity. Ar was found to have lower solubility in benzene solutions of lecithin and cholesterol than N_2 but was comparable with the solubility of oxygen in these solvent mixtures (Byrne et al., 1974). Byrne et al. likewise found increasing solubility of noble gases (xenon was not studied) in nonpolar organic solvents like xylene isomers, again consistent with the increasing lipophilicity of the larger noble gases (Byrne et al., 1975). Potter and Clynne measured the Henry's Law coefficients (a measure of solubility) of noble gases in water at a range of temperatures up to the critical point of water (Potter & Clynne, 1978). The partitioning of drugs between 1-octanol and water is a very common measure of the lipophilicity or lipid solubility of atoms and molecules. Wilcock and coworkers first measured the solubilities of He, Ne, Ar, and Kr in octanol at atmospheric pressure and temperatures spanning the physiological range (Wilcock et al., 1978). The Ostwald coefficient, the ratio of the concentration in solvent to the concentration in gas in contact with the solvent, increases with the atomic number of the noble gas. This coefficient is particularly relevant when applied to the dissolution of anaesthetic gases in blood. Ostwald coefficients for gases in water (L1) and octanol (L2) allow the estimation of logP, the log of the octanol-water partition coefficients, as log (L2/L1). Using the Ostwald coefficients the octanol-water partition coefficients can be calculated (Table 2) and compared with experimentally determined values (Abraham et al., 1994).

Ercan measured the solubility of xenon in a range of solvents and tissues, including water, saline, plasma, red blood cells and several organs (Ercan, 1979). Katz further explored the solubility of noble gases in phospholipid membranes as a potential probe for understanding membrane structure and function, prior to the discovery of useful biological effects of noble gases (Katz, 1981, 1986). The solubility of the noble gases again increased with the atomic number of the gas. A molecular thermodynamic model for the solubility of noble gases in water was reported by Braibanti et al. (1994). Katz further reported the solubilities of all of the noble gases in a wide range of organic solvents with varying degrees of lipophilicities (log octanol/water partition coefficients). These results are summarized in Table 3 and the linear relationships of solubilities with solvent lipophilicities summarized in Fig. 1.

3. Effects of noble gases on specific molecular targets

Despite chemical inertness, xenon and the other noble gases clearly display a remarkably rich spectrum of biological properties. Although there are many protein targets that noble gases may bind to, only a

Table 1
Solubility of noble gases (ml/ml) in biologically-relevant fluids at 37 °C (Weathersby & Homer, 1980).

Noble gas	Water	Plasma	Blood
He	0.00977	0.0086	0.0080, 0.0085
Ne	0.0111	…	0.0093
Ar	0.0297	0.0281	0.030
Kr	0.0504	0.051	0.060
Xe	0.0834	0.094	0.146