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REVIEWS

Therapeutic Effects of Noble Gases

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Abstract—Since the last century, it has been known that inert gases can cause a range of physiological effects. The biological activity of inert gases is an extremely multifaceted phenomenon. Despite the similarity of most physical and chemical characteristics, they differently influence many organs and tissues by interacting with a variety of protein targets. Xenon, krypton, and argon are now known to be capable of altering the functional state of the central nervous system and correcting some psychoemotional disorders. In addition, noble gases act on the processes of apoptosis and cellular stress response, affect the immune status and various homeostatic parameters. The cytoprotective effects of helium on the cardiovascular and respiratory systems have also been convincingly demonstrated. Thus, inert gases are currently being considered as potential tools to correct various diseases. This review analyzes literature data on the physiological effects of inert gases, as identified in biomedical studies on patients, as well as in cell culture and in vivo models. Each chapter is dedicated to a particular gas of this group, starting from the most studied. For each of the inert gases (helium, neon, argon, krypton, xenon, and radon), the physiological activity, possibility of being used in medicine, and some known mechanisms of its action are considered. Moreover, the existing data are critically analyzed, and the key gaps to be filled in future research are highlighted.

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INTRODUCTION

Inert or noble gases are members of a special group of the Mendeleev table, represented by one-atom gases with completely filled outer electron orbitals, which determines their absolute chemical passivity under normal conditions. Noble gas atoms are symmetrical and nonpolar, which also excludes the possibility of electrostatic interactions with biological targets. At the same time, since the middle of the last century, scientists have been aware of at least anesthetic properties of noble gases under normobaric and hyperbaric conditions [1], suggesting that their biological activity is mediated by some specific physicochemical features of these substances.

One of the characteristic features of noble gas atoms is the direct dependence of their solubility in lipids on atomic mass. It is this property that has initially been suggested as the main reason behind the anesthetic effects of noble gases in accordance with the Meyer-Overton hypothesis [2]. The noble gases, whose mass is greater than that of molecular nitrogen (Xe, Kr, Ar), possess anesthetic properties. In xenon, they are manifested at atmospheric pressure, while in krypton and argon, under hyperbaric conditions [3]. The exposure to lighter and less lipophilic noble gases (Ne, He) under hyperbaric conditions entails the development of high-pressure neurological syndrome characterized by dysmetria, myoclonic seizures, tremors, and other motor dysfunctions [4].

Using the computer methods for molecular dynamics simulations of lipid bilayers, it has been shown that heavy, anesthesia-inducing noble gases are embedded into the bilipid layer and in the hydrophobic sites of protein molecules. Small noble gases, in turn, under conditions of increased pressure, act as "solvents" that disturb the structure of the lipid-water interface, which may exactly be the reason for the development of high-pressure syndrome [5].

As said above, due to their lipophilicity, heavy noble gases are capable of not only embedding into the membrane structure but also of occupying hydrophobic sites inside protein molecules. There are plenty of methods to study the sites and energy of binding noble gas atoms to protein molecules. Studies are in progress, using both X-ray structural analysis [6] and computer modeling [7] in which binding sites are predicted with an accuracy of 1–2 van der Waals radii. For example, it has been found that noble gas atoms tend to bind to hydrophobic residues of leucine, phenylalanine and valine mainly in the corresponding pockets of protein molecules [7]. There is also a methodology for detecting protein–xenon interactions, based on large-scale measurements of stability of proteins from rates of oxidation (SPROX) and limited proteolysis (LiP) [8]. Currently, a lot of predicted noble gas–protein interactomes can be found in databases, such as RCSB (Research Collaboratory for Structural Biology) [9].

In parallel with studying the molecular dynamics of noble gas interactions with biological molecules, the integrative (systemic) aspects of their impact on the organism are being actively analyzed. Anesthetic properties of xenon have been known in physiology and medicine for about eighty years. Later studies have focused on the effects of its subanesthetic concentrations on the body, which led to the discovery of organoprotective properties of xenon and argon. This hot and promising topic has interested many scientists, and recent years have witnessed a surge in the number of publications concerned with therapeutic effects of the whole group of noble gases on the body. Among other reasons, the boom in this area owes the need to find a gas that would be a cheaper analog of xenon, while having similar protective properties. At the same time, in the wake of the growing interest in evaluating the properties of these substances, relatively new for biomedicine, studies are emerging, whose authors tend to interpret their results with a low degree of responsibility and critique. Specifically, many of them claim the presence of various "healing" properties of noble gases. However, as a rule, such conclusions are not supported by sufficiently convincing empirical calculations and are not provided with a comparison with the data by other authors. This situation is one of the reasons why it appears important and relevant to carry out a critical analysis of the literature in this area, which is the subject of the present review.

EFFECTS OF XENON

Among the noble gases, xenon was the first for which distinct physiological effects were discovered. Moreover, it is now known that, among other noble gases, xenon has the most pronounced neurotropic activity. Its effects was first demonstrated more than 80 years ago by Prof. N.V. Lazarev (Department of Pharmacology of the Kirov Military Medical Academy), who suggested that xenon has anesthetic properties [10]. Later, this suggestion was confirmed in studies on laboratory animals [2]. Since 1999, xenon has been officially approved by the Ministry of Health of the Russian Federation for use in anesthesia practice. The minimum alveolar concentration (MAC), i.e. the concentration of an inhalational anesthetic that prevents motor activity in 50% of patients in response to a standard pain stimulus, of xenon for humans is 63.1% [11], which allows its use at normal pressure. For rats, however, the MAC exceeds atmospheric pressure, amounting 161 ± 17% (the partial pressure of xenon must be 1.6 ± 0.17 atm) [3]. The anesthetic concentration of xenon positively correlates with the power of EEG slow-wave components in the frontal and parietal cortex of health volunteers [12]. Xenon anesthesia, as compared to ketamine anesthesia, is characterized by rapid awakening after anesthesia with minimal manifestations of postanesthetic symptoms and hallucinations, which is due to a deeper suppression of cerebral cortex activity [13]. However, after both xenon and sevoflurane anesthesia, the blood markers of neuronal damage were elevated in patients 1 h after its induction for lithotripsy. Total and phosphorylated Tau protein, as well as neurofilament light polypeptide (NFL), were also increased [14]. This effect may well be due to an increase in the permeability of the blood-brain barrier, which is char-

acteristic of surgery under general anesthesia [15]. Thus, xenon appears to be one of the best gas anesthetics in clinical practice. Reviews concerned with assessing xenon anesthesia efficacy indicate improved postoperative cognitive recovery in patients [16]. In addition, xenon is capable of influencing the serotoninergic system, as it can inhibit the current flowing through ionotropic serotonin receptors (5-HT3), which may control postoperative nausea and vomiting [17].

The anesthetic effect of xenon is mediated primarily by its ability to inhibit glutamatergic NMDA receptors [18]. Xenon is known to interact with the glycine site on NMDA receptors, including simultaneously both competitive and allosteric components of molecular antagonism [19]. Using computer simulation of the dynamics of xenon interaction with the glycine site, it has been shown that this site on the NMDA receptor is formed by a cavity in a protein molecule, with three aromatic amino acids, Phe 484, Phe 758, and Trp 781, being inside [20]. Upon binding to glycine, these amino acids condition the interaction with a ligand and trigger conformational changes in the NMDA receptor that mediate its activation. For xenon atoms, these amino acids create three local trapping sites formed by π-complexes of aromatic ring electrons, between which xenon atom can shuttle [21]. The xenon atom stabilizes the ligand-binding domain in an open position. Point mutations (F758W and F758Y) were found in the glycine-binding site, which level xenon affinity to this site [22].

Electrophysiological studies report the effect of xenon not only on NMDA receptors but also on other targets. In rat hippocampal cells, xenon reduced the amplitude of inward currents generated by NMDA-, AMPA-, and kainate receptors [23, 24]. Meanwhile, xenon had no effect on the currents generated by GABA receptors; however, neuronal exposure to a xenon medium entailed a decrease in the frequency of spontaneous inhibitory postsynaptic potentials, while retaining their amplitude and decay kinetics. In studies on Xenopus oocytes, xenon exhibited an inhibitory effect on α4β2 and α4β4 nicotinic acetylcholine receptors (AChRs) and, on the contrary, potentiated the α1-glycine and GABA receptors [25]. The authors speculate about the mechanisms behind the analgesic effect of xenon, however, the inhibitory effect of xenon on α4β2 AChRs contradicts their role in nociception. The article suggests that the analgesic effect of xenon appears to be mediated by its impact on NMDA receptors. In addition, xenon has been shown to influence the intracellular calcium concentration. For a number of gas anesthetics (xenon, nitrous oxide, isoflurane, and halothane), there has been shown an inhibitory effect on plasma membrane Ca^{2+}-ATPase [26]. This effect of gas anesthetics may lead to significant alterations in intracellular calcium homeostasis, increasing calcium load and potentially affecting the release of neurotransmitters [27]. However, there are contrary data, namely that xenon can inhibit long-term potentiation in mouse hippocampal neurons [28], and this effect, by contrast, is mediated by a decrease in intracellular calcium concentration due to blockade of calcium current through NMDA receptor channels. Among other mechanisms of action of xenon, there has been noted its ability to activate some of the two-pore potassium channels (TREK-1 and TASK-3), as well as ATP-sensitive potassium channels [29]. TREK-1 activation is attributed to the neuroprotective effects of xenon, i.e., suppression of glutamate excitotoxicity [30].

Among other manifestations of its neuroprotective action, xenon is capable of increasing the survival rate of neurons in mouse hippocampal slices in a model of oxygen-glucose deprivation. At the same time, neuroprotective properties of xenon disappear as glycine concentration in the medium rises [31]. In an in vivo model of brain injury, xenon led to an increase in neuronal survival and a decrease in nervous tissue inflammation, which was the reason for spatial memory improvement in animals [32]. Xenon partially, albeit sustainably, protected rat cortical neurons and septal cholinergic neurons in a rat model of Alzheimer's disease induced by cell culture exposure to L-trans-pyrrolidine-2,4-dicarboxylic acid (PDC). PDC is a synthetic analog of glutamate, evoking a mild excitotoxic stress [33]. It has also been demonstrated that xenon is able to exert neuroprotective effects complementary to memantine or ketamine, co-enhancing the suppression of excessive NMDA receptor activity.

Studies of other positive effects of xenon in subanesthetic concentrations have revealed its anticonvulsant effect both in animal models [34] and during the treatment of infants with encephalopathy [35]. Inha-

lation of xenon-containing mixtures (30% Xe) can reduce withdrawal syndrome manifestations when modeling morphine addiction in mice [36] and alcohol addiction in rats [37].

The inhibitory effect of xenon on brain cell firing can be used in the therapy of psychoemotional disorders associated with hyperactivity of brain neurons. Specifically, xenon inhalation is applied in the clinic to treat panic attacks [38], exerting an anxiolytic effect and controlling the symptoms of concomitant depressive episodes. These effects are also confirmed in studies on laboratory animals using a mouse model of lipopolysaccharide (LPS)-induced depression [39]. Xenon impaired reconsolidation of fear memories in a rat model of post-traumatic stress disorder (PTSD) [40].

In the Laboratory of General Physiology and Regulatory Peptides of the Department of Human and Animal Physiology at Lomonosov Moscow State University, experimental studies on various white rat models are in progress, focusing on neurological effects of noble gases. Specifically, our research group has demonstrated that xenon has a corrective effect on the parameters of social and depressive-like behavior when modeling autism spectrum disorders (ASD) [41].

Along with its effects on the central nervous system (CNS), xenon has been shown to exert a protective effect on other tissues and organs. It is capable of reducing myocardial infarction size in rats after ischemia-reperfusion [42]. This effect is mediated by protein kinase C-epsilon translocation and phosphorylation, as well as mitogen-activated protein kinase p38 activation, with all these molecular events being induced by xenon. According to clinical data, xenon can reduce myocardial injury in patients who have experienced out-of-hospital cardiac arrest. Inhalation of a gas mixture with a 40% concentration of xenon reduced serum troponin-T levels, which is a myocardial infarction marker [43]. In addition, xenon improved left-ventricular systolic function by increasing the ejection fraction [44].

The renoprotective effect of xenon under conditions of oxygen deprivation of human proximal tubular epithelial cell culture has also been demonstrated. In this model, xenon increased cell survival rate by increasing the expression of protein kinase B and hypoxia-inducible factor 1-alpha (HIF-1α), which provides protection under conditions of ischemic tissue injury [45]. HIF-1α can elevate blood erythropoietin levels by binding to the enhancer of its gene and activating its transcription [46]. Via this mechanism, xenon is able to induce an increase in plasma erythropoietin concentration, as well as in the total blood volume in the subjects [47, 48]. Owing to this effect, xenon is included by the World Anti-Doping Agency (WADA) in the list of drugs banned for use in professional sports [https://www.wada-ama.org/en/prohibited-list?item-id=5029, accessed on 28.05.2024].

Thus, xenon, because of its distinct neurotropic activity and organoprotective properties, is an noble gas with a wide spectrum of potential therapeutic applications. Of particular importance is its potential as a therapy for a variety of psychoemotional disorders, such as anxiety disorders, PTSD, and ASD. However, the use of noble gas in medicine involves a number of technical and economic difficulties due to its low concentration in the atmosphere and, consequently, its high cost. These circumstances dictate the need to develop better modes of using xenon during inhalation, such as the introduction of recycling systems that would allow the reuse of xenon exhaled by a patient. Increased xenon availability will contribute to the expansion of its use in the clinic.

The general trend in xenon research has a good prospect, which includes the expansion of the analysis of pharmacological activity at subanesthetic concentrations. The history of studying xenon properties is demonstrative in terms of research completeness. The analysis of the physiological effects of xenon has concerned both the molecular-dynamic basics of ligand-target interactions and its impact at a systemic level, including in vivo studies and protocols for xenon applications in the clinic. The experience of characterizing the effects of xenon may prove instrumental in the comprehensive investigation of other noble gases.

EFFECTS OF ARGON

In studying the effects of argon, the main focus was on its neuroprotective properties. In models of oxygen-glucose deprivation on cortical neurons [49–51] and hippocampal neurons [52], it has been demonstrated that argon leads to an increase in cell survival, and that its protective effect is dose- and

time-dependent. The impact of argon manifests itself in decreasing lactate dehydrogenase levels, as well as increasing the expression and translocation of the transcription factor Nrf-2 to the nucleus, in the cerebral cortex.

In addition to the works on cell cultures, there are a number of studies of argon's neuroprotective properties in in vivo models. Positive effects were shown on animals exposed to transient middle cerebral artery occlusion [50, 53, 54] and neonatal unilateral carotid artery occlusion [55]. Inhalation of argon-oxygen mixture resulted in improved neurological status and learning ability in white rats. Argon inhalation reduced the size of a lesion area in the cerebral cortex, as well as increased gene expression of the transforming growth factor beta (TGF-β) and nerve growth factor (NGF) in the penumbra area 24 h after reperfusion compared to the placebo group [54]. In a rat model of subarachnoid hemorrhage, argon also showed its protective effect that positively affected animal survival [56]. However, in the model of traumatic brain injury, argon inhalation had no effect on the volume of a lesion area [57].

A special focus is on the mechanism of argon neuroprotection, associated with changes in the activity of the innate immune system. Argon is able to reduce the density of Toll-like receptors 2 and 4 (TLR-2, TLR-4), increase phosphorylated ERK levels, and decrease the content of phosphorylated interleukin-1 receptor-associated kinase 4 (IRAK4), thus inhibiting caspase-3 activity [58]. Further studies revealed a decrease in the expression of transcription factors NF-κB and STAT3, as well as the content of their phosphorylated forms, upon exposure of human neuroblastoma cell culture to argon-oxygen mixture [59]. Argon has also been shown to decrease the expression of several pro-inflammatory factors, such as IL-1α, IL-1β, IL-6, IL-8, TNF-α, and iNOS [60]. The anti-apoptotic properties of argon have also been well characterized, specifically, the gas led to a decrease in BAX protein expression and cleaved caspase-3 levels, as well as an increase in the expression level of the apoptosis inhibitor Bcl-2 [61, 62].

A number of argon effects obviously require further investigation. For example, it has been shown that the gas decreases the level of phosphorylated protein kinase B (Akt), which is involved in cell survival-associated signaling pathways, and thus conflicts with the hypothesis of its cytoprotective effect [62]. Moreover, there is evidence that argon decreases the expression of heat shock protein HSP-70 and hemoxygenase-1, which was increased upon exposure to rotenone, a poison that disrupts the mitochondrial electron transport chain. This effect of argon is considered to be protective, but it is not abolished by the TLR-2 and TLR-4 inhibitor, suggesting that argon has a mechanism of neuroprotection unrelated to the action through innate immunity receptors. Thus, the mechanisms of argon's physiological activity remain not completely clear. Specifically, there are no data on its binding sites on protein targets. The search for these binding sites can be carried out via NMR spectroscopy and X-ray structural analysis, as was shown, e.g., for xenon [63]. Also, to visualize argon interaction with Toll-like receptors, no studies have yet been performed using molecular modeling by analogy with the description of xenon by Andrijchenko et al. [20].

Toll-like receptors play a significant role in the formation and function of the nervous system, specifically, they regulate hippocampal neurogenesis both during prenatal ontogeny and in the adult brain [64]. It has been shown that Toll-like receptor 2 knockout mice exhibit impaired cognitive functions [65]. In addition, Toll-like receptors play a significant role in neuroinflammation. For example, the pro-inflammatory cascade mediated by these receptors is triggered by alcohol ingestion, leading eventually to cell death [66]. In this regard, of particular interest is the potential ability of argon to influence CNS ontogeny and correct various disorders caused by cytotoxic effects of excessive neuroinflammation and related behavioral alterations. Currently, there is a deficit of studies concerned with argon properties in in vivo models of behavioral disorders provoked by neuroimmune activation. Furthermore, there are absolutely no studies on the offspring of laboratory animals, aimed at tracking the argon-affected developmental dynamics of the CNS since the earliest stages. At present, studies of this kind are under way in our research group at the Faculty of Biology of Lomonosov Moscow State University, with the results to be published in the near future.

Apart from neuroprotective properties, inhalation of argon-containing mixtures can exert organoprotective effects. Argon-induced pre- and postconditioning while modeling multiple organ failure led to an increase in cardiac output, as well as a decrease in

plasma creatinine levels, in rabbits. Thus, argon has cardio- and renoprotective properties [67]. Inhalation of argon-oxygen mixture during ischemia-reperfusion decreased the death of retinal ganglion cells [58] and hair cells in the rat organ of Corti [68].

In general, it can be concluded that argon causes a wide range of physiological alterations, having a cytoprotective effect in various tissues. Although no consensus on the mechanisms of action of this gas has been achieved so far, it is already clear that argon is a promising means to treat and correct multiple disorders of both the nervous and other organ systems.

EFFECTS OF HELIUM

A considerable part of helium studies is focused on its organoprotective properties. It has been shown that the gas is able to exert pre- and postconditioning effects, protecting tissues and organs from excessive degeneration. One of the mechanisms of helium neuroprotection may be associated with reducing intracellular calcium concentration, which rises due to a variety of hypoxic-ischemic brain injuries. Helium-induced preconditioning reduces calcium load by decreasing the level of ryanodine receptor 2 (RyR2) phosphorylated form, and also suppresses the expression of Ca^{2+}/calmodulin-dependent kinase II (CaMKII) and a number of necroptosis-associated proteins (RIPK-1, RIPK-3, p-MLKL) [69]. Necroptosis is one of the types of programmed cell death, in which receptor-interacting protein kinases 1 and 3 (RIPK-1, RIPK-3), as well as mixed lineage kinase domain-like pseudokinase (MLKL), play a pivotal role [70]. Necroptosis is triggered by death domain-containing (death) receptors, which transduce the signals to death-associated protein kinases (DAPKs) mediating the activation of MLKL phosphorylation. Phosphorylated MLKLs are able to form an oligomer that perforates the plasma membrane and thus induces necroptotic cell death. It is known that increased calcium overload leads to the activation of Ca^{2+}/calmodulin-dependent kinases (CaMKs), which cause RIPK-1 activation [71].

Another molecular mechanism of helium action is its ability to reduce oxidative stress in neurons [72]. Helium increases nitric oxide (NO) production, which activates Nrf-2 translocation into the nucleus. Nrf-2 is a redox-sensitive transcription factor whose signaling pathway activates the cellular antioxidant response [73]. Additionally, helium has been shown to reduce the content of pro-inflammatory proteins (TNF-α and interleukin-1β) and to increase levels of interleukin-10, brain-derived neurotrophic factor (BDNF), basic fibroblast growth factor (bFGF), and NGF, thus providing neuronal protection against inflammation and apoptosis [74].

Helium can improve the functional state of the endothelium, as demonstrated on both volunteer subjects [75] and endothelial cell cultures [76]. Its effect on the level of caveolin proteins in different tissues has been well documented. Caveolins are components involved in the formation of plasma membrane invaginations, caveolae. The structural organization of caveolae allows cells to adapt to stress, as well as regulate chaperones and signaling proteins [77]. Research shows that helium leads to dynamic changes in caveolin levels in the endothelium, brain, and heart [78]. The gas promotes caveolin-1 secretion from the endothelium, which stabilizes membranes and reduces vascular permeability. At the same time, helium is able to increase caveolin-1 and -3 expression in the rat heart, which allows this noble gas to be used as a cardioprotective agent [79]. Helium also evokes an increase in F-actin polymerization at the plasma membrane of venous endothelial cells and diminishes its polymerization in the arterial endothelium [76].

The cardioprotective effect of helium can be abolished by iberiotoxin, a blocker of mitochondrial calcium-sensitive potassium channels [80]. This allows for the conclusion that helium is able to activate this type of channels, as confirmed by a decrease in the respiratory control ratio (RCR), which is an index showing respiration and oxidative phosphorylation uncoupling in mitochondria. Helium prevents mitochondrial membrane permeabilization in the myocardium, i.e. the opening of so-called mitochondrial permeability transition pores associated with apoptosis, which increases the survival of cardiomyocytes [81]. Also in progress is the study of helium effects on cardiac fibroblasts. While causing no changes in the expression of fibroblast activation factors and the secretion level of extracellular vesicles and soluble factors, helium accelerated fibroblast migration in an in vitro glucose deprivation model [82]. However, in patients who underwent aortocoronary bypass sur-

gery, helium demonstrated no cardioprotective effect, as pre- and postconditioning had no effect on the blood troponin level and the activity of protein kinase C-epsilon, p38, ERK1/2, and HSP27 [83].

In addition to a positive effect on cardiomyocyte survival during ischemia-reperfusion, helium-oxygen mixtures can improve the functional state of the respiratory system. The use of these inhalations contributed to the improvement of spirometric indices, such as the forced expiratory volume within the first second and the maximal expiratory flow-volume, in patients with asthma [84]. Moreover, helium reduced the disease severity (assessed by the Wood's clinical asthma score), as well as the respiratory rate, during bronchospasm [85]. Meanwhile, helium inhalations had no effect on the condition of patients with chronic obstructive pulmonary disease [86].

The effect of helium on the survival of hippocampal CA-1 neurons has been studied in rat resuscitation and cardiac arrest models. However, the outcomes of these studies are contradictory, as they report both the presence of helium effects on the expression of apoptosis [78] and their absence [87]. Apparently, this may be due to different methods of modeling a heart attack, as well as differences in the methods used to assess the consequences of myocardial infarction modeling.

While being of great interest, the physiological effects of helium are the most paradoxical, as their specificity does not correlate with the standard directionality of the biological action of noble gases. The molecular mechanism of interaction between helium and its targets still remains unclear. Although numerous molecular mediators of the helium effects on cell survival have been identified, the direct reasons for their involvement are unknown. For example, the convergence of data on the decrease in intracellular calcium concentration [69] and the increase in NO levels in brain tissue homogenates [71] raises questions. The activity of constitutive NO synthases is known to increase in response to an increase in the concentration of calcium ions, which means that NO levels, on the contrary, should be expected to decrease when calcium load diminishes [88]. Meanwhile, the helium-induced increase in NO levels in brain tissue can be caused by the activation of any of the three NO synthase isoforms (neuronal, endothelial, or inducible) and, accordingly, can be regulated not only by changing calcium levels but also at the expression level, which is characteristic of inducible NO synthase. At the same time, an increase in NO concentration may also be due to a decrease in the production of reactive oxygen species, which are involved in the oxidative inactivation of NO. Thus, to elucidate the picture, it is necessary to demonstrate whether helium interacts with any of the NO synthase isoforms or with other potential regulators. The available literature on the physiological effects of helium may serve as a sound basis for further studies in this area.

EFFECTS OF RADON

Radon is the only radioactive member of the group of noble gases, which imposes certain limitations on the study of its physiological effects. According to the World Health Organization, radon can cause lung cancer in 3–14% of all cases depending on its concentration in the atmosphere [https://www.who.int/ru/news-room/fact-sheets/detail/radon-and-health Date of circulation: 30.05.2024]. At the same time, radon radioactivity promotes its relatively wide application in physiotherapy.

Radon is distributed in the atmosphere unevenly. Its concentration peaks coincide with its emission sites from uranium-bearing rocks. Radon easily diffuses from the soil, accumulating both in mines and in homes. The fact that it accumulates in mountain areas and caves has led to the booming of therapeutic resorts and sanatoriums using radon in speleo- and balneotherapy. Although there is growing body of evidence that radon therapy exerts numerous beneficial effects on the body, no randomized double-blind placebo-controlled studies are certainly being conducted, because a radon-free cave completely similar to those available at the spa territory would have to be created to meet all the standards of good clinical practice (GCP) [89].

The best known analgesic effect of radon is widely exploited in rheumatoid arthritis, ankylosing spondylitis (AS, also known as Bechterew's disease), and osteoarthritis [90]. The potential molecular mechanisms mediating this phenomenon include the involvement of transforming growth factor beta 1 (TGF-β1), β-endorphin, adrenocorticotropic hormone (ACTH), as well as a number of inflammation-associated proteins. Radon speleotherapy has been demonstrated to reduce TGF-β1 levels in AS

patients [91]. In osteoarthritis, the use of radon inhalation led to a sharp increase in β-endorphin concentration and a delayed increase in β-endorphin and ACTH levels [92]. Several studies are dedicated to the ability of radon to reduce the blood content of pro-inflammatory cytokines TNF-α [93, 94] and IL-18 [95]. Its impact on the immune system also occurs at the cellular level. The gas suppresses inflammation by reducing neutrophil and T killer counts, as well as by increasing the activity of eosinophils, dendritic cells, monocytes, and regulatory T lymphocytes (these groups of cells are involved in the restoration of tissue homeostasis in chronic inflammation) [96].

General improvement in patients with chronic diseases of the musculoskeletal system is also ascribed to a radon-mediated decrease in the intensity of bone erosion [97]. In patients after radon speleotherapy a decrease in the content of collagen fragments (CTX-I) in blood serum, a decrease in the level of adipose tissue hormone visfatin and an increase in the number of T-regulatory cells were recorded, which signals the weakening of bone tissue resorption. At the same time, the effect of radon on such indicators of bone tissue integrity as the level of parathormone in blood and the ratio of osteoprotegerin to activator of receptor of nuclear factor κB receptor (OPG/RANKL) did not differ from the effect of non-radon baths [98]. Following radon speleotherapy, patients exhibit a decrease in the serum content of type I collagen fragments (CTX-I) and the level of adipose tissue hormone visfatin, as well as an increase in regulatory T cell counts, which signals the attenuation of bone tissue resorption. Meanwhile, the effect of radon on such indices of bone tissue integrity as the blood level of parathormone and the osteoprotegerin to receptor activator of nuclear kappa factor B ligand (OPG/RANKL) ratio did not differ from the effect of regular radon-free baths [98].

There are reports on the favorable effect of radon speleotherapy on the cardiovascular system [99]. Radon decreased heart rate variability and, when combined with carbon dioxide, led to a decrease in blood pressure. There has also been documented an increase in the atrial natriuretic peptide and a decrease in vasopressin levels [91]. These effects can potentially be due to hypotensive properties of radon.

The positive effects of radon include its indirect antioxidant activity, as it has been shown that the gas activates superoxide dismutase and catalase, which prevent lipid peroxidation in cells under conditions of oxidative stress [100].

It can therefore be concluded that the information about the physiological activity of radon is as diverse as fragmentary. It remains unclear what receptor mechanisms and signaling cascades underlie changes in immune-endocrine regulation and whether these changes are interrelated. It is also yet to be elucidated whether the observed effects result from the direct action of radon atoms or from radioactive irradiation. Obviously, further basic research in this area is required, specifically, on laboratory animals. To date, there are several such works that confirm the antioxidant activity of radon in a rodent model of hepatopathy [101], as well as in the brain of intact animals [102]. However, the design of these experiments in no way correlates with the use of radon in the treatment of patients; moreover, no in vivo studies of rheumatoid arthritis have yet been performed on laboratory animal models. It is these limitations that are to be overcome in the future.

EFFECTS OF KRYPTON

The number of publications concerned with the therapeutic properties of krypton-oxygen inhalation in peer-reviewed journals is extremely low, and the available results are characterized by increased heterogeneity. At different pressures for different animal species, krypton can cause immobilization (20–30 atm for the triclad flatworm *Girardia tigrina*, 18–20 atm for the fruitfly *Drosophila melanogaster*) or anesthesia (14–16 atm for the Iberian ribbed newt *Pleurodeles walti*, 5–5.5 atm for the Japanese quail *Coturnix japonica*, and 3–3.5 atm for humans) [103, 104]. Incubation of rats in a krypton-air gas mixture at high pressure leads to an increase in the blood content of cortisol and progesterone, as well as a decrease in total thyroxine, testosterone, glucose, and urea levels. Human EEG also demonstrated spectral changes, namely a decrease in the power of α-, Δ-, and θ-waves and an increase in that of β-waves when breathing under normobaric conditions, in contrast to a decrease in the α- and β-bands and an increase in the Δ- and θ-components when breathing krypton-oxygen mixture at 2.9 atm, which

is indicative of the subjects' transition to anesthesia.

In a model of photoinduced ischemic stroke, krypton exerted a delayed neuroprotective effect, improving the neurological status in rats [105]. In this study, inhalation of krypton-oxygen mixture entailed a decrease in the penumbra zone and neuronal apoptosis, reduced the number of active microglial cells in the necrotic zone, and activated neoangiogenesis. It has been revealed that the mechanism behind the neuroprotective effect of krypton is associated with an increase in the content of phosphorylated protein kinase B and glycogen synthase-3β kinase, as well as with an increase in Nrf-2 expression and a decrease in the expression of NF-κB nuclear factor responsible, specifically, for apoptosis. Inhibitory phosphorylation of glycogen synthase-3β kinase prevents an increase in mitochondrial permeability that leads to their dysfunction and cell death due to oxidative stress.

The issue of whether krypton has physiological effects is the most debatable. There is a great paucity of pertinent publications in peer-reviewed scientific journals. The results obtained in the work by Antonova et al. [105] are promising but need to be reproduced by other research groups. That said, most of the reports and abstracts, found during the analysis of krypton-related literature, were published in non-refereed sources. While claiming that krypton has healing properties, these publications are characterized by an extremely high diversity of experimental protocols and data interpretation, and thus lack credibility. As a result, it appears difficult to assess objectively the convergence and reliability of data obtained by different authors. Therefore, further krypton studies require a deeper and more comprehensive analysis of its properties. Specifically, a screening of krypton for all types of its pharmacological activity should be carried out in the future using both cell cultures and in vivo test systems. Thus, krypton represents an unexplored but extremely promising area for physiological and pharmacological research.

EFFECTS OF NEON

Among other noble gases, neon exhibits a minimum or no intrinsic physiological properties under normobaric conditions. According to the Meyer-Overton hypothesis, extremely high pressure (80–90 atm.) is required to achieve an anesthetic effect via neon. However, such a hyperbaric application has a proconvulsant effect, causing high-pressure nervous syndrome, including tremor, myoclonic seizures, dysmetria, and other motor disorders [3]. A study of the interaction between neon atoms and biological membranes has shown that the uniformity of phospholipid bilayer arrangement is disturbed in the presence of krypton at high pressure (up to 100 bar). Also, neon has an elevated diffusivity because of the size and mass of its atom. This property allows it to migrate freely in the membrane and to increase the mobility of phospholipids, making the membrane structure less dense and ordered. Presumably, the reason for the manifestation of neon-induced neurological disorders is the generation of a so-called "noise" in the integrity of membrane structures, actually the impaired relationship between the membrane and protein complexes embedded therein [5].

As for the binding of noble gas atoms to protein molecules, the atomic size and mass play a crucial role in this case either. There is a hypothesis that the lighter members of the group of noble gases (helium and neon) have too low protein-binding energy and, hence, are unable to produce an anesthetic effect [106]. Currently, the RCSB (Research Collaboratory for Structural Biology) database annotates no protein structures neon interacts with (https://www.rcsb.org/; access date 29.05.2024). However, as mentioned above, helium, despite its small size, is able to modulate the activity of numerous receptors, transcription factors, and pro-inflammatory proteins. Consequently, the available hypotheses do not predict accurately the physiological potential of noble gases. Although by now there are no attested effects of neon, it is not possible to state with confidence that it lacks any biological activity at all. It cannot be ruled out that neon may turn out to be the only truly noble gas in its group.

CONCLUSION

At present, the search for new neuro- and organoprotective factors is an extremely urgent task of fundamental physiology and practical medicine. In this regard, the idea that noble gases have therapeutic properties definitely arouses keen interest in the scientific and medical community. The discovery of the

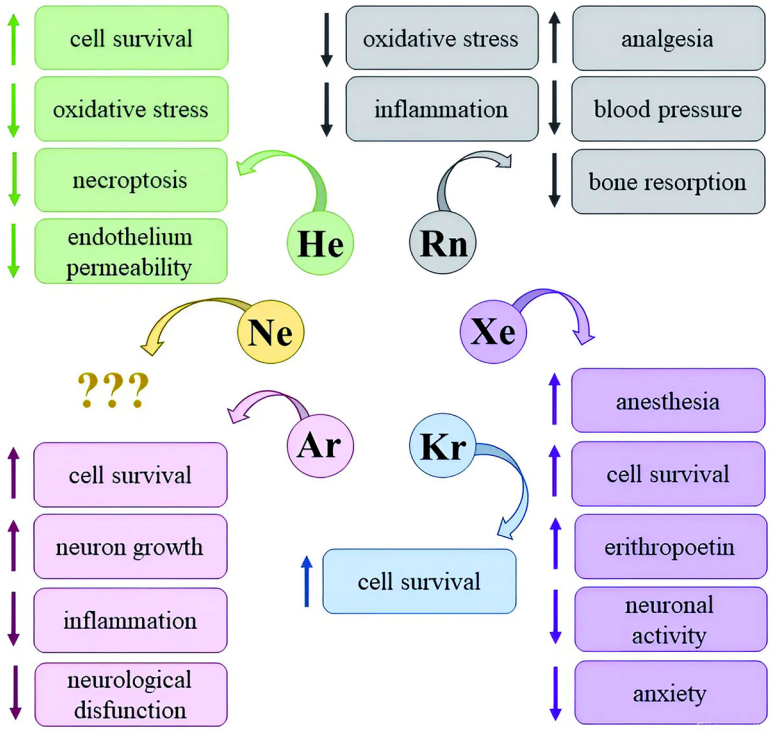

Fig. 1. Effects of noble gases, as revealed in experimental studies.

apparent physiological activity in xenon led to the study of other members of this group. Not the least role is played by economic and technical difficulties in the widespread use of xenon, which spur interest in seeking for its cheaper counterparts. Because of this, it is now known that almost all other noble gases exhibit biological activity to a greater or lesser extent (Fig. 1). For example, helium manifests cytoprotective properties, reducing the activity of necroptosis and oxidative stress in the heart and brain, argon is known for its anti-inflammatory and anti-apoptotic effects in various tissues, while radon for its analgesic properties.

However, despite the growing number of studies targeting this problem, there is still an appreciable gap between the knowledge about physiological effects of noble gases and the mechanisms of their action. For example, there are ample data on the effect of radon, xenon, argon, and helium on metabolic cascades that determine cell survival in various tissues, but only for xenon have the molecular targets that trigger actual physiological alterations been described. Moreover, there is a clear deficit of studies addressing integrative (behavioral, neuro-immuno-endocrine) effects of the noble gases. At the same time, neon and krypton represent an almost terra incognita in physiology and pharmacology.

Overall, it can be concluded that the presence of a significant cytoprotective potential in noble gases makes them a promising object for further preclinical and clinical trials aimed at expanding the medical indications for their use. Experimental studies of noble gases provide a basis for the growth of fundamental knowledge about the principles of their action on the human body, its organs, tissues, and cells.

AUTHORS' CONTRIBUTION

Conceptualization, discussion, editing the manuscript (N.U.S., V.A.D.), literature data collection and analysis, writing the manuscript (I.A.K., S.D.S.).

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ETHICS APPROVAL

This work does not contain any experimental studies on animals or humans.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflict of interest.

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