Argon: the 'lazy' noble gas with organoprotective properties

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Introduction

Sir William Ramsay and Lord Rayleigh were the first to announce the discovery of argon as a chemical element in 1895, its name being derived from the ancient Greek *ἀργόν*, *argos*, meaning lazy. The physical properties of argon, atomic number 18, are briefly outlined in this editorial. The density of argon (1.784 g dl^{-1}) is slightly heavier than nitrogen (1.251 g dl^{-1}), at 0°C .¹ The thermal conductivity of argon ($0.0178 \text{ W m}^{-1} \text{ K}^{-1}$) compared to nitrogen is lower ($0.0260 \text{ W m}^{-1} \text{ K}^{-1}$, both at 300 K).² Argon's biological activity was first described by deep sea divers in the 1930s. Their aim was to investigate gases present in the atmosphere for their suitability as respiratory gases at depth. In adventurous self-experiments, they were able to show that – under hyperbaric conditions – the narcotic effect of argon was greater than nitrogen. Yet, there was no difference detectable between argon and nitrogen with respect to respiratory resistance or psychological effects at atmospheric pressures.³ The oil/gas partition coefficient measured at 25°C is 0.14. The anaesthetic potency, as assessed by the righting reflex (ED_{50}) of argon in mice, was 15.2 atm ,⁴ considerably lower than the minimum alveolar concentration in Sprague–Dawley male rats, which was reported to be $27.0 \pm 2.6 \text{ atm}$.⁵ Nonetheless, it is obvious that argon lacks anaesthetic properties at least under normobaric conditions. Additional data on the biological activity of argon are scant but intriguing.

Neuroprotection

Russian researchers were the first to describe neuroprotective effects of argon. They assessed it in hypoxic gaseous mixtures, so-called clean agent fire extinguishing systems, in pressurised modules that made use of its fire suppression properties and were subsequently used in space vehicles. Soldatov *et al.*^{6,7} were able to show that adding argon in different concentrations (25 to 77%) to varying degrees of hypoxic gas mixtures increased

survival in the mammals who were given it to breath. Even humans exposed to hypoxia are more likely to perform complex manual and mental skills in an atmosphere containing argon rather than nitrogen.⁸

Yarin *et al.*⁹ found that exposure to an argon-oxygen atmosphere (21% O_2 /5% CO_2 /74% argon) for 48 h significantly reduced cisplatin and gentamycin-induced damage to hair cells in the newborn rat's organ of corti. Some years later, Dr Ma's team demonstrated that exposure to an atmosphere of 75% argon during and up to 24 h after injury protects cell cultures of dissociated neurons from 90 min of oxygen and glucose deprivation.¹⁰ The degree of neuroprotection offered by argon was of a similar extent to that of xenon, whereas neon and krypton did not have a protective effect, and helium, in their experimental setting, was detrimental to cells.¹⁰

In a more complex in-vitro model, Loetscher *et al.*¹¹ showed that argon was remarkably neuroprotective in hippocampal slice cultures after oxygen-glucose deprivation and traumatic brain injury. This protection was evident at concentrations of 25, 50 and 74% with the most effective protection seen at 50%. Notably, argon was effective even when applied 3 h postinjury, establishing a potential therapeutic window for possible clinical use. These findings, however, were all from in-vitro studies.

Argon's neuroprotective potential was tested by Ryang *et al.*¹² in an initial in-vivo model of transient middle cerebral artery occlusion (MCAO) in rats subjected to 2 h of focal cerebral ischaemia using the endoluminal thread model. One hour after the induction of focal cerebral ischaemia, spontaneously breathing rats received either 50% argon/50% O_2 or 50% N_2 /50% O_2 for 1 h via face-mask. Twenty-four hours after reperfusion, argon-treated animals demonstrated a significant overall reduction in infarct volumes, which, after subdivision, was most marked in the cortical and basal ganglia. In addition, argon treatment resulted in a significant improvement in the general outcome. David *et al.*¹³ assessed the effect of postinjury argon application *in vivo* in rats subjected to either an intrastriatal injection of *N*-methyl-D-aspartate (NMDA) or to occlusion of MCAO. The group found that argon, most effective in this study in a concentration of 50%, reduced brain damage by NMDA injection, and cortical brain damage induced by MCAO. In contrast to these beneficial effects at the cortical level, postinsult argon increased subcortical brain damage and failed to reduce neurological deficit. Similar to most neuroprotective strategies, in a model of MCAO, intra-ischaemic

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administration of 50% argon seemed to be superior to postischaemic.^{12,13}

In a model in which neurological injury was induced by cardiac arrest, Brücken *et al.*¹⁴ observed that rats resuscitated from 7 min of ventricular fibrillation exhibited severe neurological dysfunction. The degree of this impairment was significantly reduced for up to 7 days after arrest by the administration of 70% argon 1 h after successful resuscitation. These remarkable improvements were associated with a significant reduction in the number of necrotic neurons in the neocortex and hippocampal CA 3/4 sector.

The neuroprotective potential of argon has also been studied in neonatal hypoxic-ischaemic models. Zhuang *et al.*¹⁵ demonstrated that argon, helium and xenon, all at 70% for a duration of 90 min, given 2 h after moderate hypoxic-ischaemic encephalopathy, restored cell morphology. Here argon improved cell viability in the hippocampus compared to xenon and helium. Only argon and xenon decreased the infarction area after severe (120 min) hypoxic-ischaemic encephalopathy. Their data suggest that the neuroprotective properties of argon and xenon are superior to helium. Of note, these were the first in-vivo data to directly compare argon, helium and xenon.

Despite the wealth of studies demonstrating the benefits of argon therapy, little is known about its mechanism of action. Under hyperbaric conditions, it has been proposed that argon triggers gamma-aminobutyric acid (GABA) neurotransmission by acting at the benzodiazepine binding site of the GABA_A receptor.¹⁶ The activation of GABA receptors has been shown to be neuroprotective in both in-vitro and in-vivo models and several potential mechanisms have been proposed.^{17,18} In a computational docking simulation in human serum albumin, Seto *et al.*¹⁹ could show that argon binds to a part of the enflurane binding site. Argon's binding was dominated by van der Waals energy.

David *et al.*¹³ suggest that argon's oxygen-like properties could at least partly explain its neuroprotective action. The synergistic effect of argon on oxygen could also explain its ability to reduce NMDA-induced neuronal death, as previous data have shown redox modulation of the NMDA receptor, with inhibition of NMDA receptor activity and glutamate-induced neuronal death.¹³

Anti-apoptotic signalling appears an important mechanism of protection, for example argon increases expression of the cell survival protein.¹⁵ Furthermore, there is growing evidence that noble gases interfere with cellular signalling. The extracellular signal-regulated kinase (ERK) 1/2, a ubiquitous member of the mitogen-activated protein kinase (MAPK) family, is one of the key kinases in cellular signal transduction. Depending on the activating stimulus, it promotes a diversity of functions including activation of gene transcription programs,

cell proliferation and cell differentiation. Fahlenkamp *et al.*²⁰ were able to show that argon enhances the ERK 1/2 activity in microglia, neurons and astrocytes via the upstream kinase MEK, probably by direct activation of the MEK-ERK 1/2 pathway.

Nephroprotection

Rizvi *et al.*²¹ assessed the effect of noble gases on oxygen and glucose deprivation injury in human tubular kidney cells. Cultured human renal tubular cells (HK2) were exposed to 75% noble gas preconditioning for 3 h. Their data suggest that xenon preconditioning is protective against cell death. Argon, neon and krypton exhibited no effects on cell viability, whereas helium was cytotoxic. In contrast, Irani *et al.*²² showed a considerable potential for argon to improve the quality of grafts used for organ transplantation. The researchers addressed the question of whether a cold storage solution saturated with xenon or argon could limit ischaemia–reperfusion injury following cold ischaemia. Kidneys were harvested and stored for 6 h before transplantation. The group demonstrated that preservation of rat kidneys in argon or xenon presaturated cold storage solution decreased ischaemia–reperfusion injury, improved graft function and maintained anatomical structure.

Cardioprotection

There is evidence to suggest that brief exposure to xenon before prolonged coronary artery occlusion and reperfusion protects the myocardium against infarction.^{23–25} Pagel *et al.*²⁶ assessed whether other noble gases without anaesthetic properties would also possess properties of cardioprotection. Rabbits were subjected to a 30-min left anterior descending coronary artery occlusion after receiving three cycles of 70% argon, neon or helium for 5 min. All three gases produced cardioprotection by activating prosurvival signalling kinases and inhibiting mitochondrial permeability transition pore opening.

Future prospects

So far, no adverse or toxic effects of argon on animal or human organisms have been reported, overcoming a potential obstacle to further research. In particular, scant but intriguing data are available regarding the organ-protective properties of argon. Despite the overwhelming expertise in the field of noble gas research, mainly on xenon, the answer as to which noble gas might represent the standard, remains open. When directly compared with xenon, argon distinguishes itself in a number of ways. Specifically, its lack of sedative properties may actually be advantageous because it can be given to patients with neurological injury without interfering with their actual neurological status. Argon is the third most abundant element in our atmosphere and is about 100-fold more cost-effective than xenon. For any medical therapy, cost is a major consideration; argon may offer an affordable opportunity to improve

outcomes. Furthermore, in both in-vitro and in-vivo experiments, details such as coordinated timing, concentration and duration of application have to be probed in studies that include large animal models. In addition, the precise mechanism of argon's action remains unanswered. However, in order to translate this promising experimental data to a relevant clinical setting, experimentation must continue. As such, there is a sense of urgency to determine the role of argon in organ protection in models that incorporate pathology.^{27–32}

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