# Xenon: Neuroprotective Properties, Role in Anesthesia and Cadioprotection, Molecular Mechanisms of Action

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**Abstract**

Xenon is a noble gas that establishes neuroprotection, anesthesia and serves as a contrast agent in nuclear medicine. Its lack of side effects, safe cardiovascular and organoprotective profiles as well as effective neuroprotective role favor its applications in clinics. Xenon performs its anesthetic and neuroprotective functions through binding to glycine site of glutamatergic N-methyl-D-aspartate (NMDA) receptor competitively and blocking it. This blockage inhibits the overstimulation of NMDA receptors, preventing the following calcium accumulation cascades. Xenon is also used in combination therapies together with hypothermia. The neuroprotective effects of xenon and hypothermia cooperate synergistically whether they are applied synchronously or asynchronously. In addition, xenon demonstrates many favorable pharmacodynamic and pharmacokinetic properties, which could be used in certain clinical settings (cardiopulmonary bypass). This gas is capable of interacting with a variety of molecular targets, and some of them are modulated in anesthesia-relevant brain regions. Besides these anesthetic and analgesic effects, xenon has been shown to exert substantial organoprotective properties, especially in the brain and the heart. Several experimental studies have demonstrated a reduction in cerebral and myocardial infarction after xenon application. Distinguishing properties of xenon promise for innovations in medical gas field.


 

**Introduction to Xenon, its Physical and Chemical Properties.**

Xenon is the 54th element in the Periodic Table of the Elements and derives its name from the Greek word "stranger" (Sanders et al., 2003). It was discovered in 1898 by William Ramsay and Morris Travers in the residue left after evaporating the components of liquid air. At room temperature and atmospheric pressure xenon exists as a heavy, colorless, odorless gas but liquid and solid phases are easily obtained within an experimentally accessible range of temperatures and pressures (Cherubini et al., 2003; Cook, 1961). It presents in nature in nine stable isotopes; more than 35 unstable isotopes have been characterized ($^{133}$Xe is used as a radioisotope in nuclear medicine). Due to its fully occupied external electronic orbitals xenon is chemically inert. However, it has a low ionization potential, allowing its electron shell to be polarized by surrounding molecules. Large and highly polarisable electron cloud makes xenon strongly lipophilic (Clever, 1979). Due to its lipophilic properties liquid xenon is an ideal solvent for a number of small organic compounds (Marshall et al., 1981; Rentzepis et al., 1981), while its high polarizability gives rise to significant, but not chemically or structurally disruptive interactions between xenon and other molecules in solution. Thus, xenon can associate with aminoacids in the active site of enzymes (Prange et al., 1998; Schiltz et al., 1995; Jawad et al., 2009; Preckel et al., 2006; Esencan et al., 2013; Tilton et al., 1982; Landon et al., 2001; Spence et al., 2001; Schoenborn et al., 1965; Trudell et al., 1998; Wishnia, 1969; Ewing et al., 1970; Quillin et al., 2000; McKim et al., 1994; Anderson et al., 1993; Hasegawa et al., 1999; Brunori et al., 2001; Schiltz et al., 1994; Soltis et al., 1997) and these enzymes form a specific binding cavity for a single xenon atom without inducing major changes in protein structure. Xenon is used commercially for lasers (Maze, 2016; Patel et al., 1962), high-intensity lamps (Maze, 2016; Shuaibov et al., 2003), plasma screens (Maze, 2016; Marin, 2001), propellant in the aerospace industry (Maze, 2016; Glenn, 2008), x-ray tubes, and medical applications, including imaging (Maze, 2016; Marcucci et al., 2001; Nisticò et al., 2008; Ko et al., 2005; Coles, 2007; Latchaw et al., 2003; Wintermark et al., 2005; Kubota et al., 2012; Mountz et al., 2003; Saha et al., 1994) and anesthesia. Figure 1 summarizes xenon applications.

**Figure 1**

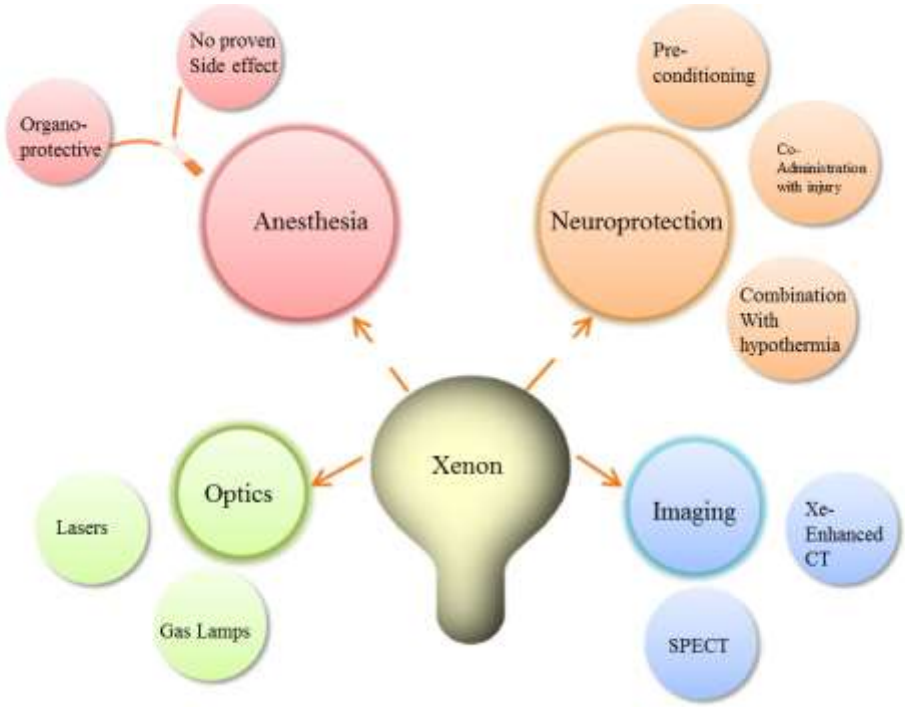


**Figure 1**. Schema summarizing xenon's applications. Noble gas xenon is used in various fields. In medicine, xenon can be utilized as a neuroprotective, anesthetic and a contrast agent. It can also be used in the field of optics (adopted from Esencan et al., 2013).

## Use of Xenon in Anesthesia

After xenon's discovery in 1898, A. R. Behnke Jr. used different breathing mixtures including xenon in his studies (Marx et al., 2000). He concluded that xenon could be used as an anesthetizing agent with the results obtained from his trials in 1939. Following this outcome, xenon was used as a surgical anesthetic agent for the first time by S. C. Cullen and Gross in 1951 (Cullen et al., 1951). This was the first report in the English literature of xenon clinical use for general anesthesia. At approximately the same time, a group of physiologists at the University of California reported xenon's anesthetic properties (Maze, 2016; Lawrence et al., 1946). Within five years, this preclinical finding was advanced to patients (Marx et al., 2000; Dworschak, 2008); it took further five decades, however, before marketing authorization was granted for the use of xenon as a general anesthetic. The Russian Federation was first to approve its use, possibly because of its notoriety as the purported anesthetic for the Russian President's heart surgery in 1996 (Maze, 2016). Since then, Western Europe has approved its use. However, xenon remains without marketing authorization for use as an anesthetic in North America. Certain factors, including its scarcity, the high cost of xenon purification from the atmosphere by fractional distillation as well as

competition posed by high-spend industries, such as aerospace make difficult to justify its value for general anesthesia. Xenon has yet to be tested for pediatric anesthesia where its potential in preventing anesthetic induced developmental toxicity may direct its use as an anesthetic for this vulnerable patient population (Maze, 2016).

As a general anesthetic, xenon possesses many advantages. It is proven that xenon doesn't have any side effects to human body (Esencan et al., 2013; Kratzer et al., 2012; Rossaint et al., 2003; Lynch et al., 2000). It has been shown *in vitro* that xenon does not cause any coagulation (Horn et al., 2001) or platelet dysfunction (de Rossi et al., 2001). It also does not deteriorate hepatic or renal functions (Bedi et al., 2003; Reinelt et al., 2002) and does not impact the immune system (Bedi et al., 2002). Besides its organoprotective property, xenon's blood-gas partition coefficient is extremely small (0.115), which results in a rapid onset and offset of its action (Esencan et al., 2013; Liu et al., 2013). It has a safe cardiovascular profile (Dworschak, 2008) and ability to penetrate through blood brain barrier without extensive effort (Kelen et al., 2010; Dworschak, 2008; David et al., 2008). These advantageous properties enable xenon to have a rapid induction, which is a key element in anesthesia (Liu et al., 2011; Dworschak, 2008). Moreover, xenon is non-teratogenic (Kelen et al., 2010) and non-fetotoxic (Joyce, 2000; Lane et al., 1980). Its lack of teratogenicity can produce profound analgesia which thereby inhibits the surgery induced hemodynamic and catecholamine responses. It is also a potent hypnotic and does not produce hemodynamic depression because it has no influence (at least in part) on some important ion channels (Jordan et al., 2010; Sanders et al., 2003). Xenon is a good candidate for being an ideal anesthetic because of not only its beneficial effects, but also its lack of toxicity. It does not have any effect on hematological and biochemical variables (Bedi et al., 2003), is non-reactive in the body and is disposed from the lungs without interfering with hepatic and renal systems, thus, not impairing hepatic or renal function (Bedi et al., 2003; Reinelt et al., 2002). Xenon has such further advantages as neuroprotective (Banks et al., 2010) and cardioprotective (Pagel, 2010; Preckel et al., 2000) effects. It has preferred hemodynamic stability (Tonner, 2006) and rapid perfusion to specific organs (Marx et al., 2000). As a result, xenon correlates with maintaining a slower heart rate and a greater arterial pressure value better than other anesthetics (Baumert, 2009). This adventitious cardiovascular profile enables the usage of xenon as an anesthetic agent during the operations on patients having coronary artery disease with tachycardia and low arterial pressure that are life threatening for them (Sprung et al., 2000).

Other than being non-hazardous to cardiovascular system, xenon can be also used as an anesthetic agent because of its additional neuroprotective role (Franks et al., 1998; Schmidt et al., 2005). Most general anesthetics induce anesthesia by potentiation of gamma-amino butyric acid receptor which is an inhibitory synaptic receptor (Esencan et al., 2013). Xenon, on the other hand, performs its anesthetic role

by blocking N-methyl-D-aspartate (NMDA) receptor similar to its neuroprotective mechanism (Franks et al., 1998; Liu et al., 2011). This blockage inhibits excitatory neurotransmission of NMDA receptors and thus, causes anesthesia. Franks et al. proved that 80% xenon decreased NMDA-activated currents by approximately 60%. Xenon's blockage of NMDA receptors enables it to have anesthetic effects, since NMDA receptors are involved in synaptic mechanisms of perception of pain, learning and memory (Franks et al., 1998). It is claimed that xenon induces anesthesia also by activating two pore domain background potassium channel TREK-1 (Sanders et al., 2005). Once activated, these channels cause neuronal hyperpolarization. Consequently, cellular excitability is decreased and anesthesia is provided (Heurteaux et al., 2004; Sanders et al., 2004). The following section reviews different mechanisms of xenon anesthetic action.

## Proposed Mechanisms for Anesthetic Action

### Receptor Effects

While several molecular targets in anesthesia-relevant brain regions are modulated by xenon, there is still no direct evidence to support one mechanism, but the role of glutamate receptors seems to be pivotal (Nagele et al., 2004; Nagele et al., 2005). Most general anesthetics act on one or more super-families of ligand-gated ion channels (Franks et al., 1994). Recent data indicate that xenon induces anesthesia in a unique way by inhibiting excitatory glutamatergic signaling (Nagele et al., 2005), although it remains unclear which subtype of glutamate-gated receptors is responsible for xenon's effects. This is certainly a feasible mechanism of anesthesia (Dildy-Mayfield et al., 1996; Krasowski et al., 1999); it also has a potential to explain the difference in potency between halogenated agents and xenon. Which of the three subtypes of postsynaptic glutamate-gated ion channels is the prime target is currently under debate; however, the current evidence firmly indicates that xenon inhibits NMDA receptor signaling by competing for binding at the glycine coactivation site (Dickinson et al., 2007) through an interaction with a phenylalanine residue (Armstrong et al., 2012). This is regarded as the prime mechanism for xenon to induce anesthesia.

Xenon has little or no effect on the inhibitory GABAA receptors in hippocampal neurons (Franks et al., 1998), which are quite sensitive to several other gaseous anesthetics (Franks et al., 1994). There is no effect of xenon on GABAergic inhibitory postsynaptic currents or on currents evoked by exogenous application of GABA in cultured neurons containing excitatory and inhibitory synapses (De Sousa et al., 2000). At the same time, in recombinant GABA receptor complexes expressed in human embryonic kidney cells xenon enhances the inhibitory GABAergic transmission (Hapfelmeier et al., 2000; Yamakura et al., 2000). In human homomeric glycine receptors xenon potentiates the current response, suggesting a contribution to the prolongation of the inhibitory postsynaptic potential (Daniels et

al., 1998). However, because xenon exerts little effect on inhibitory neurotransmission in neuronal systems, there is currently little evidence to suggest that effects at GABA and glycine receptors contribute to the xenon anesthetic state. It is shown that xenon inhibits neuronal acetylcholine (nACh) receptors responsible for modulating transmitter release in neurotransmission (Yamakura et al., 2000; Mori et al., 2001). This effect is noncompetitive and voltage independent. (Suzuki et al., 2003). It also activates TREK channels, which are proposed as a target for general anesthesia (Gruss et al., 2004; Nicoll et al., 1992; Patel et al., 2001).

Besides NMDA receptor, there are two other glutamate receptors – α-amino-3-hydroxy-5-methyl-4 isoxazolole propionate (AMPA) receptor and kainate receptor, which are called "non-NMDA receptors". Since the structures of these three glutamate receptors are very similar, both AMPA and kainate receptors are additional molecular targets for xenon (Dinse et al., 2005). Most studies confirm that xenon causes anesthesia by inhibiting NMDA receptors, whereas the studies of its effects on AMPA and kainate receptors are contradictory (Georgiev et al., 2010). In a study performed by Plested et al., the sensitivity of AMPA receptor to xenon is observed by bath application of xenon and recording the resulting ionic currents (Plested et al., 2004). When kainate is used as an artificial agonist, xenon blocks AMPA receptor due to desensitizing response elicited by kainate. When glutamate, a natural agonist of AMPA receptor is used rather than kainate xenon does not block AMPA receptor due to lack of desensitization. Therefore, it is concluded that the sensitivity of AMPA receptor to xenon depends on desensitization and that AMPA receptor is not blocked during anesthesia with xenon (Plested et al., 2004). Dinse et al., on the other hand, demonstrate by using voltage-clamped cortical neurons from embryonic mice that desensitization still occurs with the fast application of glutamate. Xenon blocks AMPA and kainate receptors even when glutamate is used as the agonist, so it is concluded that the blockage of AMPA and kainate receptors in cortical neurons contributed to xenon's anesthetic property (Dinse et al., 2005). Georgiev et al. agree that xenon performes its anesthetic action by blocking both NMDA and AMPA receptors but they claim that this blockage occurs in spinal cord dorsal horn neurons rather than cortical neurons (Georgiev et al., 2010). Thus, the role of AMPA and kainite receptors in xenon's anesthetic action is not as clear as the role of NMDA receptor (Dinse et al., 2005). Further investigations are needed for understanding xenon's anesthetic mechanisms.

**Second Messenger Signaling**

General anesthesia may result from interference at the synaptic level of $Ca^{2+}$–dependent transmitter release; in addition, modulation of second messenger systems may alter postsynaptic neuronal responses to released neurotransmitter. Changes in neuronal $Ca^{2+}$ homeostasis may alter neurotransmission in the brain and contribute to the production of the anesthetic state. It is shown that in human endothelial cells incubated with xenon only the first part

of the adenosine triphosphate–induced $Ca^{2+}$ response is observed, and the $Ca^{2+}$–dependent $Ca^{2+}$ influx is absent (Petzelt et al., 1997). These data indicate that xenon affects mechanisms regulating the $Ca^{2+}$ release–activated $Ca^{2+}$–channel of plasma membranes. The plasma membrane $Ca^{2+}$–adenosine triphosphatase (PMCA) is one $Ca^{2+}$ transport system found in neurons responsible for maintaining low cytosolic calcium concentrations (Penniston et al., 1994). It turns out that xenon inhibits PMCA pump activity, resulting in an increase in neuronal $Ca^{2+}$ concentration and alters excitability in brain synaptic plasma membranes and glioma cells (Franks et al., 1995; Singh et al., 1995). This effect presumably results from a conformational change that occurs when xenon binds to nonpolar sites inside the protein (Lopez et al., 1995) as well as non-specific interactions between the xenon and the lipid membrane (Xu et al., 1997). Xenon increases phospholipid methylation and simultaneously depresses PMCA activity (Horn et al., 1995). It also exerts some effects on second messenger signaling; however, currently it is unclear how this causally relates to the induction of anesthesia.

**Neurotransmitter Release**

The hypothalamus is a crucial homeostatic center in the brain, and the noradrenergic neuronal activity therein modulates physiologic states including consciousness and the cardiovascular system. The posterior hypothalamus is involved in the regulation of the autonomic nervous system, and an increase in norepinephrine concentration in the posterior hypothalamus increases sympathetic tone. It is shown that xenon stimulates noradrenergic neurons in the hypothalamus (Yoshida et al., 2001). This may be one mechanism contributing to the hypnotic and the sympathotonic effects of xenon. In the cerebral cortex, xenon induces an initial increase in ACh release, followed by a gradual decrease (Shichino et al., 2002). In addition, xenon had no effect on acetylcholinesterases (Ishiguro et al., 2003). Currently, the relevance of xenon's effects on the cholinergic system to the mechanisms of anesthesia, amnesia, analgesia, and organ protection requires further study.

**Neuroprotective Properties of Xenon.**

**Excitotoxicity**

Over-activation of glutamate receptors is involved in a number of pathological processes. Excessive entry of calcium, mediated by N-methyl-D-aspartate (NMDA) receptors, triggers biochemical cascades that ultimately lead to neuronal cell death. This neurotoxicity due to over-activation of NMDA receptors, termed excitotoxicity by Olney (Olney, 1969) is considered to underlie the acute neuronal injury observed following insults such as stroke, cardiac arrest, and traumatic brain injury (TBI). NMDA receptor antagonists are neuroprotective in *in vitro* and *in vivo* brain injury models (Choi et al., 1988).

Following the discovery that xenon inhibits NMDA receptors (Franks et al., 1998) it is shown that xenon can protect neuronal cell cultures against injury induced by NMDA, glutamate, or oxygen-glucose deprivation

(Wilhelm et al., 2002). The same study shows xenon to be neuroprotective *in vivo* against neuronal injury caused by subcutaneous injection of N-methyl-D,L-aspartate. Subsequently, this finding was corroborated in an *in vitro* model of hypoxia (Petzelt et al., 2003) and in an in *vivo* model of stroke (David et al., 2003). It turns out that xenon decreases acute neuronal injury in response to both the exogenous administration of excitotoxins or through deprivation of oxygen and glucose in a neuronal– glial coculture system (Wilhelm et al., 2002). *In vivo*, xenon prevents the morphologic and functional consequences of acute neuronal injury provoked by ischemia (middle cerebral artery occlusion) (Homi et al., 2003), cardiopulmonary bypass (Ma et al., 2003) and excitotoxins (Wilhelm et al., 2002).

Interestingly, recent crystallographic data on the binding of xenon to the Annexin V protein suggest that xenon may disrupt conformational changes in this protein (Dickinson et al., 2010; Colloc'h et al., 2007). Consistent with competitive inhibition at the NMDA-receptor glycine site, xenon inhibits the NMDA receptor more potently at low glycine concentrations than at high glycine concentration. Besides competitive inhibition at the glycine site, xenon has an additional noncompetitive inhibition component (Dickinson et al., 2007). It is possible that xenon's mixed competitive and noncompetitive inhibition underlies its beneficial profile compared with other NMDA receptor antagonists.

Several NMDA antagonists have been clinically evaluated for their putative neuroprotective properties. Gavestinel (with activity at the glycine co-agonist site) and magnesium sulfate (an open pore blocker) are among the most recent, but neither has sufficient efficacy, possibly because of poor central nervous system (CNS) penetrability (Haley et al., 2005; Saver et al., 2015). Other NMDA receptor antagonists, such as nitrous oxide, ketamine, and dizocilpine (MK-801) have intrinsic neurotoxicity (Ma et al., 2002). As compared, xenon not only avoids these neurotoxic effects but also ameliorates the injury produced by other NMDA antagonists (Nagata et al., 2001). It is shown that many NMDA receptor antagonists (such as ketamine and nitrous oxide) may reduce the neuronal damage after cerebral ischemia but concomitantly produce psychotomimetic side effects (Allen et al., 1990; Jevtovic-Todorovic et al., 1998). These effects are not observed, however, after xenon administration (Ma et al., 2002). A reliable marker of neuronal toxicity is the c-Fos expression in distinct cerebral regions (Gass et al., 1993). Xenon, in contrast to nitrous oxide or ketamine, does not induce c-Fos expression in the retrosplenial and posterior cingulate nuclei *in vivo* (Ma et al., 2002) and therefore, is not neurotoxic. Also, the combined use of NMDA receptor antagonists may exacerbate neurotoxicity. Nagata et al. demonstrate that nitrous oxide alone produces a small amount of c-Fos expression but significantly enhances ketamine-induced neurotoxicity (Nagata et al., 2001). In contrast, xenon alone exhibits no neurotoxicity; it reduces concentration-dependently the ketamine-

induced c-Fos expression in posterior cingulate and retrosplenial cortices, which indicates the reduction of ketamine neurotoxicity (Nagata et al., 2001). Reasons for xenon's relative lack of neurotoxicity may relate to both the site of its action on the NMDA receptor as well its neutral effect on spontaneous dopamine release that the other NMDA antagonists enhance (Sakamoto et al., 2006).

Existing data distinguish the actions of xenon as a competitive inhibitor of NMDA receptors from well-established open-channel blockers of NMDA receptors, such as ketamine and MK-801. Open-channel blockers of NMDA receptors invariably show changed kinetics following the application of the agonist in the presence of the inhibitor. For example, when NMDA is applied to NMDA receptors, the rate of closure of the channel is always much faster than that observed with an open-channel blocker, such as ketamine or MK-801 (Parsons et al., 1993). In the presence of xenon, there is no increase in the rate of NMDA response (Franks et al., 1998; Dickinson et al., 2007). Also, open-channel blockers, such as ketamine, invariably increase the decay of excitatory postsynaptic currents (Emnett et al., 2015) but this is not observed with xenon (De Sousa et al., 2000). Thus, with both heterologous expression systems and intact synapses, xenon does not behave as an open channel blocker, which may be an additional reason why it lacks neurotoxicity seen with other NMDA antagonists.

**Modulation of Background (''leak'') Potassium Conductance**

Activation of the two-pore potassium channels ($K_{2p}$ channels) tends to hyperpolarize the membrane potential, taking it farther from an activation threshold. These TREK-1 channels are the mediating mechanism by which polyunsaturated fatty acids produce neuroprotection (Honore, 2007). Genetically modified mice that lack TREK-1 channels perform poorly in models of cerebral ischemia, highlighting the importance of this molecular species in the organism's defense against acute neuronal injury (Heurteaux et al., 2004). Xenon is shown to activate the species $(TREK\text{-}1)^B$ of these channels, with activation being critically dependent on the specific amino acid residue (Glu306). It is notable that other NMDA antagonists, including nitrous oxide and cyclopropane, also activate TREK-1 (Gruss et al., 2004).

**Modulation of Neuroapoptosis**

Xenon is found to reduce neuronal apoptosis following brain injury in many models (Cattano et al., 2011; Shu et al., 2010; Yang et al., 2012). It is shown that acute neuronal ischemic injury provokes sequential waves of signalling mechanisms, which successively results in neuronal death at different times. While excitotoxicity features early in the processes, resulting in neuronal death, apoptosis (i.e., programmed cell death) follows later through signalling mechanisms that are well defined (Young et al., 2004). Xenon reduces the expression of pro-apoptotic genes, such as BAX (Ma et al., 2005) and increases the expression of

anti-apoptotic proteins, such as Bcl-xL (Ma et al., 2005) and Bcl-2 (Ma et al., 2005; Zhuang et al., 2012) resulting in a significant decline in neuroapoptosis. (Ma et al., 2005).

**Modulation of Neuroinflammation**

Several investigators have reported that circulating immune cells traverse the blood-brain barrier following acute injury (Ishikawa, et al., 2004), while the ischemic brain activates the resident microglia cells. These activated macrophages propagate the ongoing neuronal damage through the elaboration of pro-inflammatory cytokines that further injures the penumbra around an infarcted core (Arvin, et al., 1996). This process selectively prevents the spread of neuroinflammation and attenuates brain ischemic injury (Han et al., 2014a; Han et al., 2014b; Degos, et al., 2013). In several types of organ injury models, xenon has been shown to exert anti-inflammatory effects (Zhao et al., 2015; Jia et al., 2015) and decrease neuronal dysfunction associated with neuroinflammation (Vizcaychipi et al., 2011; Bessiere, et al., 2010).

**Induction of Hypoxia-Inducible factor 1alpha (HIF-1α)**

Xenon potently increases the translational efficiency and upregulation of the oxygen sensor, HIF-1α, under normoxic conditions (Ma et al., 2009). Downstream effectors of HIF-1α, including erythropoietin (EPO), have been shown to exert important neuroprotective properties (Merelli et al., 2013). Nevertheless, it should be emphasized that, when EPO is administered to patients with anemia due to diabetes-induced renal failure, there is a twofold increase in stroke (Pfeffer et al., 2009). In the setting of organ injury, xenon-induced upregulation of HIF-1α has been shown to be cytoprotective in the kidney (Ma et al., 2009; Zhao et al., 2013), (Degos, et al., 2013) lung, heart (Goetzenich et al., 2014) and brain (Patel et al., 1962) without producing any side effects.

**Modulation of Adenosine Triphosphate (ATP)-sensitive Potassium Channels ($K_{ATP}$ Channels)**

Recently, xenon has been shown to activate another potassium channel, the plasmalemmal ATP-sensitive potassium ($K_{ATP}$) channel (Dickinson et al., 2010; Bantel et al., 2009). $K_{ATP}$ channels are inhibited by physiological levels of ATP and act as sensors of metabolic activity. In neurons, $K_{ATP}$ channels are activated under conditions of physiological stress such as hypoxia. Activation of $K_{ATP}$ channels reduces neuronal excitability and is protective against ischemic injury (Ballanyi, 2004). Clinical concentrations of xenon activate $K_{ATP}$ channels by up to 50%, and this activation may mediate xenon preconditioning against ischemic injury (Bantel et al., 2009). Hypoxic-ischemic neuronal injury can be also preempted by activation of $K_{ATP}$ channels (Sun et al., 2015; Qu et al., 2015; Dickinson et al., 2010; Haseneder et al., 2009) and the absence of activation exacerbates cerebral ischemic injury (Li et al., 2013). Pre-treatment with xenon prevents glucose- and oxygen-deprived neuronal cells from dying in primary cultures. A key mechanism

involves xenon's activation of the $K_{ATP}$ channels (Bantel et al., 2009; Bantel et al., 2010).

**Modulation of neuronal nicotinic acetylcholine (nACh) receptors**

Other ion channels that appear to be sensitive to xenon are neuronal nicotinic acetylcholine (nACh) receptors and 5-hydroxytryptamine type 3 (5-$HT_3$) receptors. Neuronal nACh receptors, composed of $\alpha_4\beta_2$ subunits, and homomeric $\alpha_7$ subunits are inhibited by xenon, while $\alpha_4\beta_4$-containing receptors are insensitive to it (Dickinson et al., 2010; Yamakura, et al., 2000; Suzuki et al., 2003). Although nACh receptors are inhibited by a number of anesthetics at clinically relevant concentrations, it is unclear whether this inhibition has any role in mediating general anesthesia. Neuronal nACh receptors have been implicated in neuroprotection (Bencherif, 2009); it is unclear, however, whether the inhibition of nACh receptors by xenon plays a role in xenon neuroprotection. Xenon inhibits human 5-$HT_3$ receptors expressed in *Xenopus* oocytes by ~65% at clinical concentrations (Suzuki et al., 2002), but the clinical significance of this observation is still unclear.

**Cellular and Molecular Mechanisms of Neuroprotection**

Xenon exerts its neuroprotective effect through an antiapoptotic mechanism (Ma et al., 2005) and does not produce apoptotic neurodegeneration (Williamson et al., 2004). On the basis of existing data, xenon's neuroprotective action seems to be mediated via antiapoptotic pathways. Exposure to xenon doubles the number of viable cells, and this improvement exclusively results from a reduction in the amount of apoptosis. Necrotic cell death, on the other hand, is not reduced with xenon exposure. A similar antiapoptotic effect of xenon is noted when acute neuronal injury is provoked by NMDA exposure or by oxygen–glucose deprivation. Xenon's antiapoptotic effect is also confirmed in *in vivo* studies. In rat pups injured by hypoxia– ischemia, xenon alone, as well as a neuroprotective combination of subtherapeutic interventions with xenon (20%) and hypothermia (35°C), significantly increased cell viability by decreasing apoptosis as assessed by morphologic criteria.

Hypothermia is the only therapeutic intervention that has, so far, been shown to provide even a modicum of neuroprotection in the clinical setting (Bernard et al., 2002); therefore, it is worth determining the possible convergence of hypothermia and xenon on similar signaling pathways. When applied individually, both xenon and hypothermia reduce acute neuronal injury after oxygen–glucose deprivation. When applied together, the neuronal protection provided by the combination is significantly greater than could be expected from a simply additive interaction. Such a synergistic interaction with hypothermia may be a unique feature of xenon because it is not present with another NMDA receptor antagonist, gavestinel. Xenon also interacts synergistically with isoflurane, another anesthetic capable of providing neuroprotection. Neuroprotection of

isoflurane is at least in part a result of GABAA receptor stimulation (Ma et al., 2003b), and the potentiated neuroprotective effect of a combination with xenon may be due to their differing mechanisms of action. Consistent with this concept, NMDA-induced $Ca^{2+}$ influx, which is thought to be a critical event involved in excitotoxic neuronal death (Goldberg et al., 1993), is reduced after administration of xenon in cortical cell cultures (David et al., 2003).

In addition to the effects mediated *via* the NMDA receptor, xenon protects cortical neurons against hypoxia- related cell damage *via* $Ca^{2+}$-dependent mechanisms (Petzelt et al., 2003). Petzelt et al. demonstrated xenon-induced neuroprotection in dopaminergic neurons (Petzelt et al., 2004). Nerve growth factors that include D1- and D2-dopamine receptors differentiate pheochromocytoma cells (PC-12 cells) and release dopamine as a result of increased release and reduced uptake rate of dopamine after hypoxia. This dopamine release is linked to cellular damage as evidenced by lactate dehydrogenase release from the cells. Xenon prevents the dopamine release in PC-12 cells induced hypoxia, and this neuroprotective effect is reduced after buffering intracellular $Ca^{2+}$ using a $Ca^{2+}$ chelator (Petzelt et al., 2004). This is of special interest because NMDA antagonist neurotoxicity has been linked to excess dopaminergic activation (Ma et al., 2002) and xenon, which itself lacks toxicity (Ma et al., 2002) and protects against ketamine induced neurotoxicity (Nagata et al., 2001) seems to prevent dopamine induced toxicity.

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The role of dopamine in the mechanism of NMDA antagonist toxicity and xenon's neuroprotective effects requires further investigation.

In a neuronal– glial cell coculture, pre-exposure to xenon causes a concentration-dependent reduction of lactate dehydrogenase release from cells deprived of oxygen and glucose (Preckel et al., 2006). Thus, preconditioning with xenon decreases oxygen–glucose deprivation. However, xenon's preconditioning effect is abolished by cycloheximide, a protein synthesis inhibitor (Ma et al., 2006). In an *in vivo* model of neonatal asphyxia involving hypoxic– ischemic injury preconditioning with xenon reduces infarction size and gives rises to sustained improvement in neurologic function. Contrastingly, no preconditioning is observed with nitrous oxide (Ma et al., 2006). From *in vivo* experiments, quantitative immunoblotting reveals that the phosphorylated $Ca^{2+}$/cAMP-responsive element binding protein and brain-derived neurotrophic factor (Ma et al., 2006) are significantly up-regulated after xenon exposure, with a time course similar to that of the preconditioning response; this provides an important clue as to which signaling pathways are involved. Neither brain derived neurotrophic factor nor the phosphorylated $Ca^{2+}$/cAMP-responsive element binding protein levels changed after nitrous oxide exposure (Ma et al., 2006) as opposite to xenon. The molecular effects of xenon on the central nervous system are summarized in table 1 and Figure 2.

**Table 1. Molecular Effects of Xenon on the Central Nervous System** (adopted from Preckel et al., 2006)

Noncompetitive blockade of *N*-methyl-D-aspartate receptors (Franks et al., 1998; Yamakura et al., 2000)

Inhibition of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor after stimulation by kainate, but not by glutamate (Plested et al., 2004)

Potentiation of the current response of glycine receptors (Yamakura et al., 2000; Daniels et al., 1998)

Blockade of *N*-acetyl-choline receptors (Yamakura et al., 2000; Suzuki et al., 2003)

No effect on acetylcholinesterase in rat brain tissue *in vitro* (Ishiguro et al., 2003)

Competitive blockade of 5-hydroxytryptamine type 3A receptors (Suzuki et al., 2002)

Activation of two-pore-domain potassium channels TREK-1 (Gruss et al., 2004)

Inhibition of plasma membrane $Ca^{2+}$ adenosine triphosphatase pump activity (Franks et al., 1995; Singh et al., 1995; Horn et al., 1995)

Stimulation of norepinephrinergic neurons (Yoshida et al., 2001)

Increased cyclic guanosine monophosphate levels in spinal cord, brainstem, and hippocampus in rats (Galley et al., 2001)

Suppression of spinal cord dorsal horn neurons (Utsumi et al., 1997; Miyazaki et al., 1999)

Antiapoptotic effect (Ma et al., 2005; Williamson et al., 2004)

Preconditioning effect (Ma et al., 2006)

Lack of neurotoxicity (Ma et al., 2002)

$Ca^{2+}$-dependent neuroprotection in dopaminergic neurons and embryonic cortical neurons (Petzelt et al., 2003)

**Figure 2**

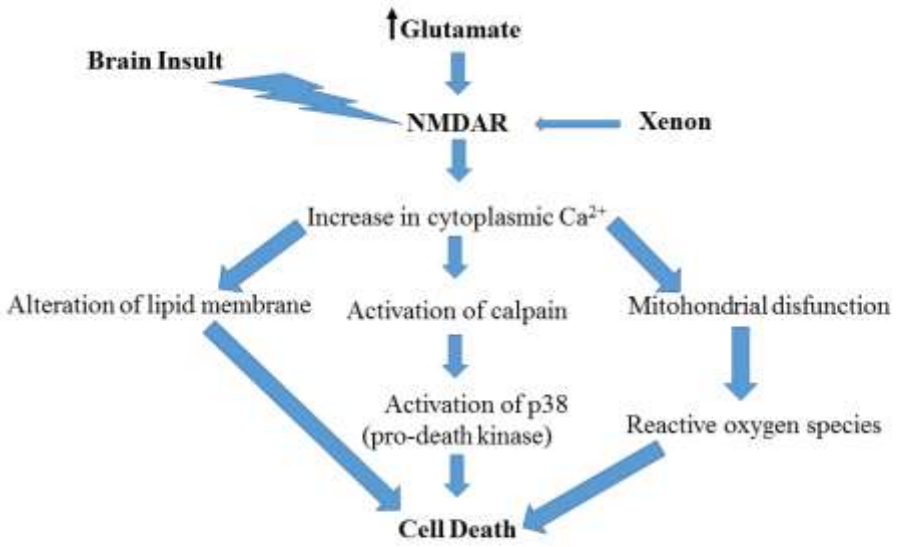


**Figure 2**. Mechanism of xenon's neuroprotective action. The neuroprotective effect of xenon is based on blockage of NMDA receptors. Without xenon blockage, increase in cytoplasmic calcium concentration due to overstimulation of NMDA receptors leads to cell death by various pathways. Xenon inhibits these cascades by competitively binding to glycine site of NMDA receptors (adopted from Esencan et al., 2013).

## Effects of Xenon as Related to Specific Clinical Conditions

Maze, 2016 has a detailed summary of the preclinical studies assessing the effects of xenon in models of acute neurological injury. The studies address various medical conditions for which use of xenon may be beneficial, including neonatal hypoxic ischemic encephalopathy (HIE) from intrapartum asphyxia, stroke, traumatic brain injury (TBI), anestheticinduced develop-pmental toxicity, and cardiac arrest. Below we discuss some aspects of these studies that delineate the uniqueness of xenon action and beneficiary of its application.

### Cardioprotection

Xenon has post-conditioning cardio-protective effect (Preckel et al., 2006). Thus, it reduces the infarct size after regional myocardial ischemia in rabbits *in vivo* (Preckel et al., 2000). It can also induce cardioprotection *via* the pre-conditioning mechanism in ischemia (Preckel et al., 2006). Ischemic preconditioning describes the protection of myocardial tissue against infarction by short, non-lethal periods of ischemia. In the past years, the halogenated (volatile) anesthetics, *e.g.*, isoflurane (Cason et al., 1997; Mu¨llenheim et al., 2002) or sevoflurane (Mu¨llenheim et al., 2003), have been recognized to mimic the strong


 

cardioprotection exerted by ischemic preconditioning (pharmacologic or anesthetic-induced preconditioning). Pharmacologic activation of different receptors mimics ischemic preconditioning and activates inhibitory G proteins (Kirsch et al., 1990) and protein kinase C (PKC) (Figure 3) (Speechly-Dick et al., 1995). This activation of PKC affects other signaling pathways, such as Raf-MEK1-MAP kinases and the PI3-kinase-Akt cascade (Takahashi et al., 1999). Moreover, the release of free radicals activates different kinases, including PKC (mainly its ε-isoform) (Yang et al., 1997), tyrosine kinases (Baines et al., 1998), and mitogen- activated protein kinases (MAPKs) (Weinbrenner et al., 1997), which act as triggers and/or mediators of the resulting cardioprotection (for review, see Das *et al.* 1999). Recent data indicate that xenon is able to induce pharmacologic preconditioning of the heart *in vivo*. Thus, xenon inhalation results in a significant reduction of the infarct size compared with controls (Preckel et al., 2006). Calphostin C, an inhibitor of PKC, and SB203580, an inhibitor of p38 MAPK abolishe the preconditioning effects of xenon. These data suggest that PKC and p38 MAPK are key mediators of xenon-induced preconditioning. PKC-ε is one of the isoforms present in cardiac myocytes and is mainly implicated in preconditioning mechanisms. PKC isoforms have been shown to be mainly regulated *via* translocation to different cell compartments and subsequent phosphorylation, resulting in their activation. By use of a phosphospecific antibody against PKC-ε, it is demonstrated that xenon leads to a marked phosphorylation of PKC-ε compared with controls (Uecker et al., 2003). PKC-ε translocates from cytosolic to membrane regions upon different stimuli; xenon increases the amount of PKC-ε in the membrane fraction. It is shown (Preckel et al., 2006) that there is no influence of xenon preconditioning on phosphorylation of PKC-ε at different time points during the preconditioning protocol, suggesting an isoform specific activation of PKC-ε by xenon. Calphostin C abolished the effect of xenon on PKC-ε phosphorylation, which also implies isoform specific activation.

Activation of PKC affects other downstream signaling pathways like the MAPK cascade, and in this context, it has been shown that PKC-ε interacts with MAPK during cardioprotection. Xenon induces a significant increase of p38 MAPK phosphorrylation and calphostin C abrogates this effect, demonstrating that p38 MAPK is located downstream of PKC in the signaling cascade of xenon-induced preconditioning (Weber et al., 2005a). p38 MAPK is suggested to interact with the actin cytoskeleton *via* the MAPK-activated protein kinase-2 (MAPKAPK-2) and heat shock protein (HSP)27 (Figure 3). Xenon preconditioning induces phosphorylation of MAPKAPK-2 and HSP27, and both effects could be blocked by calphostin C and SB203580. Xenon enhances the translocation of HSP27 to the particulate fraction and increases F-actin polymerization. F-actin and HSP27 are colocalized after xenon preconditioning (Weber et al., 2005b). These data show that xenon induces cardioprotection by

preconditioning and that activation of PKC-ε and its downstream target p38 MAPK are central molecular mechanisms involved. Xenon activates MAPKAPK-2 and HSP-27 downstream of PKC and p38 MAPK, and these data link preconditioning by xenon in the myocardium to the actin cytoskeleton.

**Figure 3**

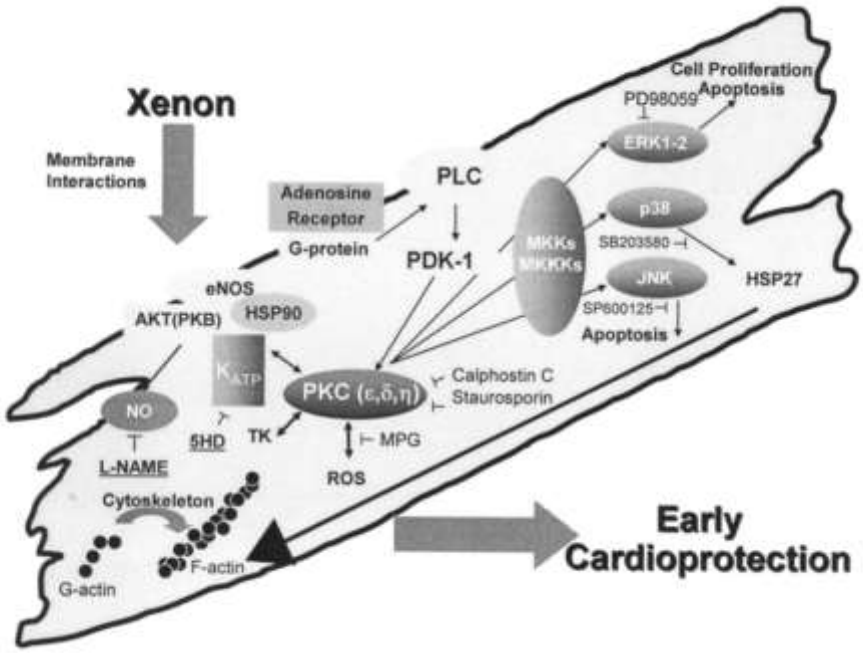


**Figure 3**. Preconditioning by xenon involves the activation of protein kinase C (PKC) (adopted from Preckel et al., 2006).

It is demonstrated (Preckel et al., 2006) that both the p44/42 MAPK (extracellular signal–regulated kinase, ERK) and the stress-activated p54/46 MAPK (SAPK/JNK) participate to in xenon induced preconditioning (Weber et al., 2005c). Both kinases play a key role in differentiation and cell survival as well as in apoptosis regulation. The ERK inhibitor PD 98059 completely abolishes the observed cardioprotection offered by xenon, demonstrating an involvement of ERK 1/2 in the signal transduction. Interestingly, SP 600125, a JNK inhibitor, has no effect on infarct size reduction by xenon. In addition, the phosphorylation state of SAPK/JNK is not influenced by xenon (Weber et al., 2005c). These data suggest that besides the p38 MAPK, also ERK is involved in xenon preconditioning. However, the third member of the MAPK family, the SAPK/ JNK, is not a mediator of xenon preconditioning, suggesting a highly specific regulation of different kinases by xenon in the myocardium.

Several investigators have demonstrated the existence of a second episode of myocardial protection (late preconditioning), which begins 12–24 h after the preconditioning stimulus and lasts for 48–72 h (Preckel et al., 2006). In contrast to early pre-conditioning, the phenomenon of late preconditioning is long thought not to be induced by halogenated anesthetics (Kehl et al., 2002). Interestingly, there exists increasing evidence from different *in vivo* models that isoflurane, sevoflurane, and desflurane produce a second window of cardioprotection (Lutz et al., 2004; Wakeno-Takahashi et al., 2005; Smul et al., 2005). Preliminary results show (Preckel et al., 2006) that xenon also induces late cardioprotection similar to ischemic late preconditioning. However, the molecular mechanisms behind this xenon-induced late cardioprotection remain unknown and need further investigation. Molecular effects of xenon on the heart are summarized in Table 2.

**Table 2. Molecular Effects of Xenon on the Cardiovascular System** (adopted from Preckel et al., 2006)

| |
|---|
| Slight inhibition of transient outward currents of voltage-gated K+ channels (Hu¨neke et al., 2001) |
| Preconditioning of the heart via PKC and p38 mitogen-activated protein kinase (Weber et al., 2005c) |
| Myocardial preconditioning via extracellular signal–regulated kinase ½ (Weber et al., 2005a) |
| No effect on PKC-α, PKC-δ, and stress-activated p54/46 MAPK after xenon preconditioning (Wirthle et al., 2005; Weber et al., 2005a) |
| Phosphorylation and translocation of PKC-ε (Weber et al., 2005c) |
| Phosphorylation of p38 mitogen-activated protein kinase downstream of PKC (Weber et al., 2005c) |
| Phosphorylation of mitogen-activated protein kinase–activated protein kinase-2 and heat shock protein (Yamakura et al, 2000; Weber et al., 2005b) |
| Translocation of heat shock protein 27 and F-actin polymerization (Weber et al., 2005b) |
| Blockade of $Ca^{2+}$-dependent $Ca^{2+}$ influx in endothelial cells (Petzelt et al., 1997) |

**Hypoxia–ischemia. *In vivo* Studies.**

Recent *in vivo* studies on sub-anesthetic dosage of xenon with 50% concentration have promising results against neonatal hypoxia-ischemia (Esencan et al., 2013; Liu et al., 2011), cardiac arrest (CA) induced cerebral ischemia (Fries et al., 2008) and neurobehavioral dysfunction caused by brain insult (Parsons et al., 2000). Major mechanisms lying behind xenon's neuroprotective property are the reduction of ischemia-induced neurotransmitter release (Dinse et al., 2005) as well as the antagonistic property against NMDA receptors (Fries et al., 2008; Chakkarapani et al., 2009; Natale et al., 2006) (Figure 2). It has been proven by Franks and colleagues that xenon's property of being antagonist to

NMDA receptors is a key factor (Franks et al., 1998), since NMDA receptors are primarily involved in initiation and progression of apoptosis in neural tissue (Sanders et al., 2005; Hardingham et al., 2003). Fries et al. state that after xenon treatment, there is a reduction of perivascular inflammation in putamen and caudate nucleus on pigs with post CA (Fries et al., 2008). In addition, Dingley et al. show short-term neuroprotective effects of xenon administration in neonatal rats which are exposed to hypoxia-ischemia (Dingley et al., 2006; Liu et al., 2011). Also, it is demonstrated that preconditioning of xenon displays neuroprotective effects like reducing the size of infarction and enhancing neurological functions in neonatal rats having hypoxia-ischemia (Liu et al., 2011; Ma et al., 2006). It has also been indicated that xenon has a higher efficacy in cortex rather than subcortex due to the difference in vascularity and in density of NMDA receptors in two distinct layers of cerebrum (Homi et al., 2003). Another beneficial property of xenon is its non-toxic chemical characteristic which enables the usage of the gas on neonates. The high risk of any traumatic event during childbirth brings the idea of xenon preconditioning to mother as a method of reducing the possibility of brain insult to the neonate (Luo et al., 2008). Xenon is an ideal gas for this model due to its cardiovascular stability (Coburn et al., 2005) and myocardial protection property (Preckel et al., 2002), as well as its rapid induction rate through blood–brain-barrier (Kelen et al., 2010; Goto et al., 1997). Due to these favoring characteristics, clinical usage of xenon for neuroprotection was approved in Europe in 2007 (Spieth et al., 2001; Derwall et al., 2009). Focal cerebral ischemia, in which a blood clot occludes blood vessels of the brain (Smith, 2004), is commonly induced by *in vivo* animal model called filament occlusion of middle cerebral artery (MCAO) (Homi et al., 2003). It has been indicated that application of xenon during MCAO in mice reduces total infarct size and augments neurologic outcome (David et al., 2008; Sanders et al., 2005; Homi et al., 2003). Besides its co-administration with the injury, its preconditioning also provides neuroprotection in mice model of MCAO (Horiguchi et al., 2006).

**Hypoxia–ischemia. *In vitro* Studies.**

Oxygen glucose deprivation (OGD) is one of the *in vitro* models of ischemia. It is a condition that neurons undergo after the insult when cerebral blood flow is disrupted. This deprivation activates excitoxicity in which NMDA glutamate receptors are overstimulated, leading to neuronal death through apoptosis and necrosis (David et al., 2008). It has been shown that xenon reduces neuronal injury by its administration before and during the insult (Rizvi et al., 2010; Ma et al., 2006; Wilhelm et al., 2002). Bantel et al. demonstrated neuronal preconditioning property of xenon by exposing neuronal-glial co-cultures to 75% xenon for 2 hours (Bantel et al., 2009). Another study held by Maleeha et al. (Esencan et al., 2013) showed that xenon preconditioning protects human kidney cells from OGD injury. They proposed the mechanism in which survival factors p-Akt, HIF-1a and Bcl-2 are upregulated (Rizvi et al., 2010). Xenon also

acts as a neuro-protectant when co-administered with OGD injurious agents. It has been shown that xenon reduces OGD induced neuronal cell death in neuronal-glial cell co-culture at sub-anesthetic concentrations. Since lactate dehydrogenase release is an indication for cell injury, xenon's mentioned neuroprotective role has been assessed by the reduction in lactate dehydrogenase release (Liu et al., 2011; Wilhelm et al., 2002). Helene et al. also prove that xenon reduces lactate dehydrogenase and dopamine release, the latter being a key event in excitotoxicity in OGD (David et al., 2008). This again shows that xenon attenuates neuronal injury when it is co-administered with OGD.

**Synergistic Interaction Between Xenon and Therapeutic Hypothermia**

Currently, hypothermia is the only intervention that provides neuroprotection after hypoxia-ischemia (Chakkarapani et al., 2009; Tooley et al., 2003; Gunn et al., 2006; Gluckman et al., 2005). It has been proven that it enhances neurological outcome after hypoxia-ischemia not only in neonatal rats, pigs, and sheep but also in infants who suffer from hypoxic ischemic encephalopathy (Kelen et al., 2010) and adults after out-of-hospital CA (Thoresen et al., 2009). Hypothermia makes it possible to reduce neurological deficits for one out of six infants with neonatal encephalopathy (Gluckman et al., 2005; Thoresen et al., 2009). To increase this ratio, drugs able to enhance hypothermia's neuroprotection should be investigated. Xenon is a promising candidate for this role because of its lack of chemical reactivity and side effects, non-fetotoxicity and easy reversibility (Chakkarapani et al., 2009).

Studies have shown that xenon augments neuroprotection when combined with hypothermia in animal hypoxia-ischemia models (Dingley et al., 2006; Chakkarapani et al., 2010). There are convincing scientific data to extend the potential neuroprotective properties of xenon to settings in which therapeutic hypothermia/targeted temperature management (TH/TTM) is provided. All data published to date show that xenon's neuroprotective action is most effective when body temperature is reduced. Unlike other neuroprotective strategies, including different NMDA antagonists (gavestinel), xenon alone exhibits this enhanced efficacy when temperature is reduced. To determine the possible mechanism for the superior neuroprotection that xenon provides in the presence of hypothermia, further studies are performed *in vitro* using an oxygen-glucose deprivation model to induce ischemic damage (lactate dehydrogenase release) in cultured neurons (Ma et al., 2005). It has been demonstrated that a combination therapy of hypothermia (32°C) with inhalation of 50% xenon for 3 hours increases neuroprotection from 37% (hypothermia only) to 76% (hypothermia combined with xenon inhalation) (Hobbs et al., 2008; Chakkarapani et al., 2010). The synergistic neuroprotective effect of this treatment is still obtained even after asynchronous administration of xenon and hypothermia. When xenon (20%) and hypothermia (35°C) are applied asynchronously with 1 hour and 5 hour gap in between the treatments, their

neuroprotective effect still combine synergistically and brain infarction in neonatal rat hypoxia-ischemia model is reduced significantly (Martin et al., 2007).

Hypothermia decreases the release of glutamate that binds to NMDA receptors. It also reduces the release of glycine which assists glutamate to act on the NMDA receptor. Since xenon is a NMDA receptor antagonist, hypothermia's role of decreasing neurotransmitter and xenon's role of receptor blockage converge on an antiapoptotic pathway (Hobbs et al., 2008). This mechanism might also explain why asynchronous administration of xenon and hypothermia still improves the neurologic outcome of hypoxia-ischemia (Kelen et al., 2010).

It has also been studied whether a combination therapy of xenon with other drugs like dexmedetomidine and sevoflurane is effective against hypoxia-ischemia. Combination of xenon with dexmedetomidine reduces OGD induced brain infarction *in vivo* (Rajakumaraswamy et al., 2006). Also, OGD injury is decreased *in vivo* by independent preconditioning of xenon and sevoflurane (Ma et al., 2006; Luo et al., 2008). Yan et al. have shown that combination of xenon and sevoflurane preconditioning induces long term neuroprotection in neonatal asphyxia. This combination gives the chance to apply drugs in lower doses in the presence of xenon (Luo et al., 2008).

**Clinical Studies of Neurological Injury Treated with a Combination of Xenon and TH** (cited from Maze, 2016)

**For patients undergoing coronary artery bypass grafting while on cardio-pulmonary bypass**

There is an increased incidence of postoperative neurocognitive deficit (POCD) following cardiac surgery with cardiopulmonary bypass (CPB) (Newman et al., 2001). Moreover, the pathogenic mechanisms involved in the development of POCD may be similar to those involved in the propagation of acute neuronal injury from other causes (Lynch et al., 2002). Hence, xenon has been investigated as a potential prophylactic pharmacological intervention (Lockwood et al., 2006). To test the feasibility and safety of delivering xenon to patients undergoing coronary artery bypass graft surgery while on CPB, xenon is administered to patients in an open-label dose-escalation study (0, 20, 35, 50% xenon in oxygen and air; n = 4 per group). Xenon is delivered throughout the surgical portion of the procedure, including prior to, during, and after CPB. Xenon concentration (partial pressures) is measured at five defined points before, during, and after CPB using gas chromatography. Because of a theoretical concern regarding gas bubble emboli, middle cerebral artery Doppler is used to assess embolic load. Blood markers, S100-b and troponin I, are also used to assess adverse effects of emboli on major organ system function. Xenon is delivered at the chosen partial pressures using a closed-circle breathing system that recirculated the gas after scrubbing out the carbon dioxide

and supplementing oxygen to ensure adequate oxygenation. Patients administered xenon have no major organ dysfunction, while xenon increases gas diffusion (Reinelt et al., 2001). This small open-label trial shows the tolerability of xenon in patients with cardiac disease and is an important precursor for the subsequent Xe-hypotheca study.

**Xenon and therapeutic hypothermia for out-of-hospital cardiac arrest (OHCA)**

The Xe-hypotheca study is a Phase II drug clinical trial in adult victims of OHCA with an initial cardiac rhythm that is ‘‘shockable’’, i.e., either ventricular fibrillation or pulseless ventricular tachycardia. One hundred ten patients are randomized in a 1:1 ratio to receive either mild therapeutic hypothermia treatment alone for 24 hr (MTH group) or in combination with inhaled xenon. A report of the feasibility and safety of the first 36 patients enrolled in the trial has been published (Arola et al., 2013).

After assessment and emergent treatment (i.e., mechanical ventilation and correction of cardiovascular instability) in the emergency department, patients undergo a brain computerized tomography scan and transthoracic echocardiography to exclude a possible cerebral origin of the cardiac arrest and to assess myocardial function. If an ST-elevation myocardial infarction is established, primary percutaneous coronary intervention is performed before ICU admission. Subsequent care is performed according to the Utstein style, and the recommendations of the International Liaison Committee on Resuscitation are followed (Langhelle et al., 2005).

Cooling of patients is conducted with the use of an Alsius CoolGardTM 3000 thermal regulation system (Zoll Medical Corporation, Chelmsford, MA, USA), an invasive intravascular temperature management device, to achieve a target core temperature of 33°C and then to maintain the core temperature for 24 hr. Subsequent rewarming is performed at a maximum rate of $0.5°C \cdot hr^{-1}$. Sedation is accomplished with a continuous infusion of propofol (1-5 $mg \cdot kg^{-1} \cdot hr^{-1}$) and fentanyl (50-100 $\mu g \cdot hr^{-1}$), and shivering is terminated with cisatracurium. Exposure to xenon is accomplished through a PhysioFlexTM closed system ventilator (Dra¨ger, Lu¨beck, Germany) to achieve an end-tidal xenon concentration of at least 40%. This is delivered continuously until completion of rewarming. At the time of the first report, no adverse reactions attributable to xenon are identified (Arola et al., 2013). The favorable cardiovascular features, together with the use of xenon at higher concentrations in surgical settings (albeit for shorter durations), portend safe use of xenon when combined with mild therapeutic hypothermia in patients with cardiovascular disease.

**Hypoxic ischemic encephalopathy**

The 2010 International Liaison Committee on Resuscitation guidelines state that infants born at (or near) term with moderate to severe HIE should be offered therapeutic hypothermia. Treatment should be initiated and conducted under clearly defined

protocols at neonatal intensive care facilities that provide multidisciplinary care and follow-up (Perlman et al., 2010). A meta-analysis that included 767 neonates concluded that therapeutic hypothermia significantly reduced the risk of death or disability at 18 months vs standard care. The number needed to treat of neonates for one newborn to be free of death or disability is 9 (Edwards et al., 2010). Thus, the therapeutic benefit of hypothermia is modest and further neuroprotective interventions are urgently needed. Studies have evolved to identify adjunctive agents that have focused around the use of EPO and xenon. While early studies had shown the safety and possible additional benefit of EPO treatment (Elmahdy et al., 2010; Wu et al., 2012) randomized trials need to be undertaken with this adjuvant. The current evidence is insufficient to recommend adjunctive EPO therapy for newborns with HIE who are undergoing hypothermia.

For the use of xenon as an adjunctive to therapeutic hypothermia, two groups have independently pursued clinical studies to ascertain the dose range, duration, feasibility, and safety (Maze, 2016). The investigators have reported preliminary findings regarding the potentially beneficial effect of xenon on seizure activity (Azzopardi et al., 2013). These data are very encouraging because the severity of seizures in asphyxiated encephalopathic neonates is strongly associated with more extensive brain injury (Miller et al., 2002) and worse clinical outcome (Glass et al., 2009).

**Anesthetic-induced developmental neurotoxicity**

Despite the reversible nature of general anesthesia, when immature organisms are exposed to compounds that produce the anesthetized state, brain injury can occur and result in long-term neurobehavioral deficits (Jevtovic-Todorovic et al., 2003). This anesthetic-induced developmental neurotoxicity (AIDN) is unlikely due to physiological derangements that may accompany the anesthetized state because blood gas tensions are normal (Yon et al., 2005) and anesthetic-induced toxicity can be reproduced in *in vitro* neuronal cell cultures (Twaroski et al., 2014) as well as in *ex vivo* brain slices (Ma et al., 2007; Wise-Faberowski et al., 2005; Spahr-Schopfer et al., 2000). Indeed, this AIDN has been noted with structurally unrelated compounds spanning the entire panoply of general anesthetic agents approved for pediatric use (Jevtovic-Todorovic et al., 2003; Kodama et al., 2011; Satomoto et al., 2009; Fredriksson et al., 2007; Bercker et al., 2009). It is also evident across species – from nematodes (Gentry et al., 2013) to rodents (Jevtovic-Todorovic et al., 2003) to piglets (Schubert et al., 2012) as well as to non-human primates (Zou et al., 2011; Paule et al., 2011; Creeley et al., 2013; Creeley et al., 2014; Brambrink et al., 2012).

In contrast to the preponderance of preclinical studies establishing AIDN, this has yet to be confirmed in well controlled prospective randomized clinical trials. In fact, observational data obtained from databases collected for other reasons (Ing et al., 2014; Sprung et al., 2012) represent the

most compelling support for an association between exposure to general anesthesia and subsequent cognitive and behavioral problems later in human life. This association is strongest for multiple anesthetics administered to children younger than three years (Flick et al., 2011).

Based on the known neuroprotective effects of xenon, the question whether xenon itself produces AIDN and whether it can prevent AIDN has been addressed in several studies (Ma et al., 2007; Cattano et al., 2008; Sabir et al., 2013; Shu et al., 2010; Brosnan et al., 2013). Apart from the *in vitro* preparation in which concentrations of xenon above 1 MAC produced injury, each of the studies in neonatal rats, neonatal mice, and piglets showed attenuation of anesthetic-induced neurotoxicity and/or lack of AIDN when exposure to xenon is included (Ma et al., 2007; Cattano et al., 2008; Sabir et al., 2013; Shu et al., 2010). Nevertheless, it is noteworthy that xenon alone did produce significant, albeit modest, neuroapoptosis (though less than isoflurane) when administered alone to mice (Cattano et al., 2008) However, xenon attenuated the injury produced by isoflurane in this species, as well as in other species (Cattano et al., 2008).

**Traumatic brain injury**

Approximately 1.7 million patients per year require medical care in the United States for TBI, incurring an annual medical cost burden of over $70 billion (Maze, 2016). The severity of the condition is highlighted by the fact that 1/3 of injury-related deaths are caused by TBI. The next imperative, following effective strategies to prevent TBI from concussive and blast assaults, is to acquire effective neuroprotective measures to salvage potentially surviving neurons from progressive damage and cell death. Earlier *in vitro* work on brain slice preparations showed significant neuroprotection with administered xenon (Coburn et al., 2008). A recent *in vivo* study of a TBI model in rats (Campos-Pires et al., 2015) showed significant reduction in contusion volume, improved neurological outcome scores, and enhanced long-term locomotor function. Further studies are required to investigate the role of xenon in neuroprotection in TBI.

**Stroke**

Following the demonstration that intervention for a prehospital stroke can be delivered in the field (Saver et al., 2015), the stage is set for extending xenon's use to a ''field setting''. Members of emergency medical services are quite skilled at securing the necessary airway to administer inhalation therapy at the site where the patient is first encountered, long before admission to the emergency department. It would not be necessary to rule out intracranial hemorrhage as a cause for the stroke. According to the best available evidence to date, xenon appears to be equally effective and non-toxic for both hemorrhagic and non-hemorrhagic causes of stroke (Sheng et al., 2012).

**Other Molecular Effects Exerted by Xenon**

In embryonic rat brain astroglial cells, xenon produces a block of the cell cycle at

metaphase, and this effect is completely reversible by slightly increasing intracellular $Ca^{2+}$ concentration (Preckel, 2006; Petzelt et al., 1999a). In human endothelial cells, the block in the cell cycle is at the $G_2$–M transition and at metaphase, again reversible by increasing intracellular $Ca^{2+}$ concentration (Petzelt et al., 1999b). Therefore, xenon interferes with $Ca^{2+}$-dependent regulatory systems, but so far, no specific event or defined regulatory complex of the $Ca^{2+}$ signaling system has been identified.

In human whole blood *in vitro*, xenon does not affect the unstimulated or agonist-induced platelet glycoprotein expression, the activation of the glycoprotein IIb/IIIa receptor, or the platelet-related hemostasis, suggesting no altered platelet function (De Rossi et al., 2001). An investigation on neutrophil and monocyte function demonstrates no effect on the respiratory burst activity of these cells but an increased phagocytosis activity of neutrophils (De Rossi et al., 2002). Therefore, xenon preserves neutrophil and monocyte antibacterial capacity *in vitro*. Selectins are involved in the initial contact between neutrophils and endothelial cells. Xenon increases the removal of selectins from neutrophil surface, thereby probably inhibiting the adhesion of neutrophils to the endothelium (De Rossi et al., 2004a). This might have implications in the recruitment of neutrophils to an inflammatory site. In addition, adhesion molecule receptors are involved in the pathophysiology of ischemia–reperfusion injury. Xenon administration during reperfusion reduces myocardial infarct size after regional ischemia in rabbits (Preckel et al., 2000) and modulation of neutrophil function may be an underlying mechanism. Adhesion molecules facilitate leukocyte migration into injured tissue. However, expression of adhesion molecules on mice brain endothelial cells is not affected by 75% xenon, suggesting no anti-inflammatory actions at the vascular endothelium (Yamamoto et al., 2003). In an isolated cardiopulmonary bypass system, xenon has no immunomodulatory effects and does not change interleukin-8 or interleukin-10 levels (Bedi et al., 2002). In human monocytes *in vitro*, xenon increases the lipopolysaccharide- induced production of tumor necrosis factor α and interleukin-6 and activated nuclear transcription factor κB in contrast to isoflurane (De Rossi et al., 2004b).

## Conclusion

Xenon has a promising future in medicine due to its noticeable advantages over other anesthetic agents. Its neuro- and myocardio-protective profile, non-toxic chemical properties, nature friendly feature and efficacy in hypoxia-ischemia treatment combined with hypothermia makes it an ideal candidate for innovations in medical gas field. Promising findings obtained from *in vivo-vitro* studies of xenon denote that xenon will take its part in neuroprotective treatments for brain trauma, resuscitation and ischemic insults. However, further research and large-scale investigations are necessary to utilize xenon's therapeutic potential.

**Bibliography**

Allen, H.L., Iversen, LL., 1990. Phencyclidine, dizocilpine, and cerebrocortical neurons (letter). Science 247, 221

Anderson, D.E., Hurley, J.H., Nicholson, H., Baase, W.A., Matthews, B.W., 1993. Protein Sci. 2, 1285.

Armstrong, S.P., Banks, P.J., McKitrick, T.J., et al., 2012. Identification of two mutations (F758W and F758Y) in the N-methyl-D-aspartate receptor glycine-binding site that selectively prevent competitive inhibition by xenon without affecting glycine binding. Anesthesiology 117, 38-47.

Arola, O.J., Laitio, R.M., Roine, R.O., et al., 2013. Feasibility and cardiac safety of inhaled xenon in combination with therapeutic hypothermia following out-of-hospital cardiac arrest. Crit Care Med 41, 2116-24.

Arvin, B., Neville, L.F., Barone, F.C., Feuerstein, GZ., 1996. The role of inflammation and cytokines in brain injury. Neurosci Biobehav Rev 20, 445-52.

Azzopardi, D., Robertson, N.J., Kapetanakis, A., et al., 2013. Anticonvulsant effect of xenon on neonatal asphyxial seizures. Arch Dis Child Fetal Neonatal Ed 98, F437-9.

Baines, C.P., Wang, L., Cohen, M.V., Downey, J.M., 1998. Protein tyrosine kinase is downstream of protein kinase C for ischemic preconditioning's anti-infarct effect in the rabbit heart. J Mol Cell Cardiol 30, 383–92

Ballanyi, K., 2004. Protective role of neuronal KATP channels in brain hypoxia. J Exp Biol 207, 3201-3212.

Banks, P., Franks, N.P., Dickinson, R., 2010. Competitive inhibition at the glycine site of the N-methyl-D-aspartate receptor mediates xenon neuroprotection against hypoxia-ischemia. Anesthesiology 112, 614–622.

Bantel, C., Maze, M., Trapp S., 2009. Neuronal preconditioning by inhalational anesthetics: evidence for the role of plasmalemmal adenosine triphosphate-sensitive potassium channels. Anesthesiology 110, 986-995.

Bantel, C., Maze, M., Trapp, S., 2010. Noble gas xenon is a novel adenosine triphosphate-sensitive potassium channel opener. Anesthesiology 112, 623-30.

Baumert, J.H., 2009. Xenon-based anesthesia: theory and practice. Open Access Surgery 2, 5–13.

Bedi, A., McBride, W.T., Armstrong, M.A., Murray, J.M., Fee JPH., 2002. Xenon has no effect on cytokine balance and adhesion molecule expression within an isolated cardiopulmonary bypass system. Br J Anaesth 89, 546–550.

Bedi, A., Murray, J.M., Dingley, J., Stevenson, M.A., Fee, J.P.H., 2003. Use of xenon as a sedative for patients receiving critical care. Crit Care Med 31, 2470–2477.

Bencherif, M., 2009. Neuronal nicotinic receptors as novel targets for infl ammation and neuroprotection: mechanistic considerations and clinical relevance. Acta Pharmacol Sin 30, 702-714.

Bercker, S., Bert, B., Bittigau, P., et al., 2009. Neurodegeneration in newborn rats following propofol and sevoflurane anesthesia. Neurotox Res 16, 140-7.

Bernard, S.A., Gray, T.W., Buist, M.D., Jones, B.M., Silvester, W., Gutteridge, G., Smith, K., 2002. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346, 557–63

Bessiere, B., Laboureyras, E., Laulin, J.P., Simonnet, G., 2010. Xenon prevents inflammation-induced delayed pain hypersensitivity in rats. Neuroreport 21, 1167-71.

Brambrink, A.M., Evers, A.S., Avidan, M.S., et al., 2012. Ketamine-induced neuroapoptosis in the fetal and neonatal rhesus macaque brain. Anesthesiology 116, 372-84.

Brosnan, H., Bickler, P.E., 2013. Xenon neurotoxicity in rat hippocampal slice cultures is similar to isoflurane and sevoflurane. Anesthesiology 119, 335-44.

Brunori, M., Gibson, Q.H., 2001. EMBO Rep. 2, 674.

Campos-Pires, R., Armstrong, S.P., Sebastiani, A., et al., 2015. Xenon improves neurologic outcome and reduces secondary injury following trauma in an in vivo model of traumatic brain injury. Crit Care Med 43, 149-58.

Cason, B.A., Gamperl, A.K., Slocum, R.E., Hickey, R.F., 1997. Anesthetic-induced preconditioning: Previous administration of isoflurane decreases myocardial infarct size in rabbits. Anesthesiology 87, 1182–90

Cattano, D., Williamson, P., Fukui, K., et al., 2008. Potential of xenon to induce or to protect against neuroapoptosis in the developing mouse brain. Can J Anesth 55, 429-36.

Cattano, D., et al., 2011. Xenon exposure in the neonatal rat brain: effects on genes that regulate apoptosis. Minerva Anestesiol. 77, 571–578.

Chakkarapani, E., Thoresen, M., Hobbs, C.E., Aquilina, K., Liu, X., Dingley, J., 2009. A closed-circuit neonatal xenon delivery system: a technical and practical neuroprotection feasibility study in newborn pigs. Anesth Analg 109, 451–460.

Chakkarapani, E., Dingley, J., Liu, X., Hoque, N., Aquilina, K., Porter, H., Thoresen, M., 2010. Xenon enhances hypothermic neuroprotection in asphyxiated newborn pigs. Ann Neurol 68, 330–341.

Cherubini, A., Bifone, A., 2003. Hyperpolarized xenon in biology. Prog. Nuclear Mag. Reson. Spect. 42, 1–30.

Choi, D.W., Koh, J.Y., Peters, S., 1988. Pharmacology of glutamate neurotoxicity in cortical cell culture: attenuation by NMDA antagonists. J Neurosci 8, 185-96.

Clever, H.L., 1979. Krypton, Xenon and Radon—Gas Solubilities, vol. 2, Pergamon Press, Oxford.

Coburn, M., Kunitz, O., Baumert, J.-H., Hecker, K., Haaf, S., Zühlsdorff, A., Beeker, T., Rossaint, R., 2005. Randomized controlled trial of the haemodynamic and recovery effects of xenon or propofol anaesthesia. Br J Anaesth 94, 198–202.

Coburn, M., Maze, M., Franks, N.P., 2008. The neuroprotective effects of xenon and helium in an in vitro model of traumatic brain injury. Crit Care Med 36, 588-95.

Coles, J.P., 2007. Imaging after brain injury. Br J Anaesth 99, 49–60.

Colloc'h, N., Sopkova-de Oliveira Santos, J., Retailleau, P., Vivares, D., Bonnete, F., Langlois d'Estainto, B., Gallois, B., Brisson, A., Risso, J.J., Lemaire, M., Prange, T., Abraini, J.H., 2007. Protein crystallography

under xenon and nitrous oxide pressure: comparison with in vivo pharmacology studies and implications for the mechanism of inhaled anesthetic action. Biophys J 92, 217-224.

Cook, G.E., 1961. Argon, Helium and the Rare Gases. Interscience Publishers, New York.

Creeley, C., Dikranian, K., Dissen, G., Martin, L., Olney, J., Brambrink, A., 2013. Propofol-induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain. Br J Anaesth 110, i29-38.

Creeley, C.E., Dikranian, K.T., Dissen, G.A., Back, S.A., Olney, J.W., Brambrink, A.M., 2014. Isoflurane-induced apoptosis of neurons and oligodendrocytes in the fetal rhesus macaque brain. Anesthesiology 120, 626-38.

Cullen, S.C., Gross, E.G., 1951. The anesthetic properties of xenon in animals and human beings, with additional observations on krypton. Science 113, 580-2.

Daniels, S., Roberts, R.J., 1998. Post-synaptic inhibitory mechanisms of anaesthesia: Glycine receptors. Toxicol Lett 101, 71–6

Das, D.K., Engelman, R.M., Maulik, N., 1999. Oxygen free radical signaling in ischemic preconditioning. Ann N Y Acad Sci 874, 49–65

David, H.N., Leveille, F., Chazalviel, L., et al., 2003. Reduction of ischemic brain damage by nitrous oxide and xenon. J Cereb Blood Flow Metab 23, 1168-73.

David, H.N., Haelewyn, B., Rouillon, C., Lecoq, M., Chazalviel, L., Apiou, G., Risso, J.-J., Lemaire, M., Abraini, J.H., 2008. Neuroprotective effects of xenon: a therapeutic window of opportunity in rats subjected to transient cerebral ischemia. FASEB J 22, 1275–1286.

De Rossi, L.W., Horn, N.A., Baumert, J.H., Gutensohn, K., Hutschenreuter, G., Rossaint, R., 2001. Xenon does not affect human platelet function in vitro. Anesth Analg 93, 635.

De Rossi, L.W., Gott, K., Horn, N.A., Hecker, K., Hutschenreuter, G., Rossaint, R., 2002. Xenon preserves neutrophil and monocyte function in human whole blood. Can J Anesth 49, 942–5

De Rossi, L.W., Horn, N.A., Stevanovic, A., Buhre, W., Hutschenreuter, G., Rossaint R., 2004a. Xenon modulates neutrophil adhesion molecule expression *in vitro*. Eur J Anaesthesiol 21, 139–43

De Rossi, L.W., Brueckmann, M., Rex, S., Barderschneider, M., Buhre, W., Rossaint, R., 2004b. Xenon and isoflurane differentially modulate lipopolysaccharide induced activation of the nuclear transcription factor KB and production of tumor necrosis factor-a and interleukin-6 in monocytes. Anesth Analg 98, 1007–12

De Sousa, S.L.M., Dickinson, R., Lieb, W.R., Franks, N.P., 2000. Contrasting synaptic actions of the inhalational general anesthetics isoflurane and xenon. Anesthesiology 92, 1055–66

Degos, V., Vacas, S., Han, Z., et al., 2013. Depletion of bone marrow derived macrophages perturbs the innate immune response to surgery and reduces postoperative memory dysfunction. Anesthesiology 118, 527-36.

Derwall, M., Coburn, M., Rex, S., Hein, M., Rossaint, R., Fries, M., 2009. Xenon: recent

developments and future perspectives. Minerva Anestesiol 75, 37–45.

Dickinson, R., Peterson, B.K., Banks, P., et al., 2007. Competitive inhibition at the glycine site of the N-methyl-D-aspartate receptor by the anesthetics xenon and isoflurane: evidence from molecular modeling and electrophysiology. Anesthesiology 107, 756-67.

Dickinson, R., Franks, N.P., 2010. Critical Care 14, 229.

Dildy-Mayfield, J.E., Eger, E.I. II, Harris, R.A., 1996. Anesthetics produce subunitselective actions on glutamate receptors. J Pharmacol Exp Ther 276, 1058–65

Dingley, J., Tooley, J., Porter, H., Thoresen, M., 2006. Xenon provides short-term neuroprotection in neonatal rats when administered after hypoxiaischemia. Stroke 37, 501–506.

Dinse, A., Föhr, K.J., Georgieff, M., Beyer, C., Bulling, A., Weigt, H.U., 2005. Xenon reduces glutamate-, AMPA-, and kainate-induced membrane currents in cortical neurones. Br J Anaesth 94, 479–485.

Dworschak, M., 2008. Pharmacologic neuroprotection–is xenon the light at the end of the tunnel? Crit Care Med 36, 2477–2479.

Edwards, A.D., Brocklehurst, P., Gunn, A.J., et al., 2010. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ 340, c363.

Elmahdy, H., El-Mashad, A.R., El-Bahrawy, H., El-Gohary, T., ElBarbary, A., Aly, H., 2010. Human recombinant erythropoietin in asphyxia neonatorum: pilot trial. Pediatrics 125, e1135-42.

Emnett, C.M., Eisenman, L.N., Mohan, J., et al., 2015. Interaction between positive allosteric modulators and trapping blockers of the NMDA receptor channel. Br J Pharmacol 172, 1333-47.

Esencan, E., Simge, Y., Tosun, B. Y., Robinot, A., Solaroglu, I., Zhang, J.H., 2013. Xenon in medical area: emphasis on neuroprotection in hypoxia and anesthesia Medical Gas Research 3, 4.

Ewing, G.J., Maestas, S., 1970. J. Phys. Chem. 74, 2341.

Flick, R.P., Katusic, S.K., Colligan, R.C., et al., 2011. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics 128, e1053-61.

Franks, N.P., Lieb, W.R., 1994. Molecular and cellular mechanisms of general anesthesia. Nature 367, 607–14

Franks, J.J., Horn, J.-L., Janicki, P.K., Singh, G., 1995. Halothane, isoflurane, xenon, and nitrous oxide inhibit calcium ATPase pump activity in rat brain synaptic plasma membranes. Anesthesiology 82, 108–17

Franks, N.P., Dickinson, R., de Sousa, S.L.M., Hall, A.C., Lieb, W.R., 1998. How does xenon produce anaesthesia? Nature 396, 324–324.

Fredriksson, A., Ponten, E., Gordh, T., Eriksson, P., 2007. Neonatal exposure to a combination of N-methyl-D-aspartate and gammaaminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. Anesthesiology 107, 427-36.

Fries, M., Nolte, K.W., Coburn, M., Rex, S., Timper, A., Kottmann, K., Siepmann, K.,

Häusler, M., Weis, J., Rossaint, R., 2008. Xenon reduces neurohistopathological damage and improves the early neurological deficit after cardiac arrest in pigs. Crit Care Med 36, 2420–2426.

Galley, H.F., Le, Cras, A.E., Logan, S.D., Webster, N.R., 2001. Differential nitric oxide synthase activity, cofactor availability and cGMP accumulation in the central nervous system during anaesthesia. Br J Anaesth 86, 388–94

Gass, P., Herdegen, T., Bravo, R., Kiessling, M., 1993. Induction and suppression of immediate early genes in specific rat brain regions by the non-competitive N-methyl-D-aspartate receptor antagonist MK-801. Neuroscience 53, 749–58

Gentry, K.R., Steele, L.M., Sedensky, M.M., Morgan, P.G., 2013. Early developmental exposure to volatile anesthetics causes behavioral defects in Caenorhabditis elegans. Anesth Analg 116, 185-9.

Georgiev, S.K., Furue, H., Baba, H., Kohno T., 2010. Xenon inhibits excitatory but not inhibitory transmission in rat spinal cord dorsal horn neurons. Mol Pain 6, 25.

Glass, H.C., Glidden, D., Jeremy, R.J., Barkovich, A.J., Ferriero, D.M., Miller, S.P., 2009. Clinical neonatal seizures are independently associated with outcome in infants at risk for hypoxicischemic brain injury. J Pediatr 155, 318-23.

Glenn Research Center, NASA, 2008. Fact Sheet: Innovative Engines: Glenn Ion Propulsion Research Tames the Challenges of 21st Century Space Travel.

Gluckman, P.D., Wyatt, J.S., Azzopardi, D., Ballard, R., Edwards, A.D., Ferriero, D.M., Polin, R.A., Robertson, C.M., Thoresen, M., Whitelaw, A., Gunn, A., 2005. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet 365, 663–670.

Goetzenich, A., Hatam, N., Preuss, S., et al., 2014. The role of hypoxiainducible factor-1alpha and vascular endothelial growth factor in late-phase preconditioning with xenon, isoflurane and levosimendan in rat cardiomyocytes. Interact Cardiovasc Thorac Surg 18, 321-8.

Goldberg, M.P., Choi, D,W., 1993. Combined oxygen and glucose deprivation in cortical cell culture: Calcium-dependent and calcium-independent mechanisms of neuronal injury. J Neurosci 13, 3510–24

Goto, T., Saito, H., Shinkai, M., Nakata, Y., Ichinose, F., Morita, S., 1997. Xenon provides faster emergence from anesthesia than does nitrous oxide-sevoflurane or nitrous oxide-isoflurane. Anesthesiology 86, 1273–1278.

Gruss, M., Bushell, T.J., Bright, D.P., Lieb, W.R., Mathie, A., Franks, N.P., 2004. Two-poredomain K+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. Mol Pharmacol 65, 443–52

Gunn, A.J., Thoresen, M., 2006. Hypothermic neuroprotection. NeuroRx 3, 154–169.

Haley, E. Jr., Thompson, J.L., Levin, B., et al., 2005. Gavestinel does not improve outcome after acute intracerebral hemorrhage: an analysis from the GAIN International and GAIN Americas studies. Stroke 36, 1006-10.

Han, Z., Li, L., Wang, L., Degos, V., Maze, M., Su, H., 2014a. Alpha-7 nicotinic acetylcholine receptor agonist treatment

reduces neuroinflammation, oxidative stress and brain injury in mice with ischemic stroke and bone fracture. J Neurochem 131, 498-508.

Han, Z., Shen, F., He, Y., et al., 2014. Activation of alpha-7 nicotinic acetylcholine receptor reduces ischemic stroke injury through reduction of pro-inflammatory macrophages and oxidative stress. PLoS One 9, e105711.

Hapfelmeier, G., Zieglgansberger, W., Haseneder, R., Schneck, H., Kochs, E., 2000. Nitrous oxide and xenon increase the efficacy of GABA at recombinant mammalian GABAA receptors. Anesth Analg 91, 1542–9

Hardingham, G.E., Bading, H., 2003. The Yin and Yang of NMDA receptor signalling. Trends Neurosci 26, 81–89.

Hasegawa, J., Shimahara, H., Mizutani, M., Uchiyama, S., Arai, H., Ishii, M., Kobayashi, Y., Ferguson, S.J., Sambongi, Y., Igarashi, Y., 1999. J. Biol. Chem. 274, 37533.

Haseneder, R., Kratzer, S., Kochs, E., Mattusch, C., Eder, M., Rammes, G., 2009. Xenon attenuates excitatory synaptic transmission in the rodent prefrontal cortex and spinal cord dorsal horn. Anesthesiology 111, 1297-1307.

Heurteaux, C., Guy, N., Laigle, C., Blondeau, N., Duprat, F., Mazzuca, M., Lang-Lazdunski, L., Widmann, C., Zanzouri, M., Romey, G., Lazdunski, M., 2004. TREK-1, a K+ channel involved in neuroprotection and general anesthesia. EMBO J 23, 2684–2695.

Hobbs, C., Thoresen, M., Tucker, A., Aquilina, K., Chakkarapani, E., Dingley, J., 2008. Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ ischemia. Stroke 39, 1307–1313.

Homi, H.M., Yokoo, N., Ma, D., Warner, D.S., Franks, N.P., Maze, M., Grocott, H.P., 2003. The neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. Anesthesiology 99, 876–81

Honore, E., 2007. The neuronal background K2P channels: focus on TREK1. Nat Rev Neurosci 8, 251-61.

Horiguchi, T., Snipes, J.A., Kis, B., Shimizu, K., Busija, D.W., 2006. Cyclooxygenase-2 mediates the development of cortical spreading depression-induced tolerance to transient focal cerebral ischemia in rats. Neuroscience 140, 723–730.

Horn, J.-L., Janicki, P.K., Franks, J.J., 1995. Nitrous oxide and xenon enhance phospholipid-N-methylation in rat brain synaptic plasma membranes. Life Sci 56, PL455–60

Horn, N.A., Hecker, K.E., Bongers, B., Baumert, H.J., Reyle-Hahn, S.M., Rossaint R., 2001. Coagulation assessment in healthy pigs undergoing single xenon anaesthesia and combinations with isoflurane and sevoflurane. Acta Anaesthesiol Scand 45, 634–638.

Hu¨neke, R., Ju¨ngling, E., Skasa, M., Rossaint, R., Lu¨ckhoff, A., 2001. Effects of the anesthetic gases xenon, halothane, and isoflurane on calcium and potassium currents in human atrial cardiomyocytes. Anesthesiology 95, 999–1006

Ing, C.H., DiMaggio, C.J., Malacova, E., et al., 2014. Comparative analysis of outcome

measures used in examining neurodevelopmental effects of early childhood anesthesia exposure. Anesthesiology 120, 1319-32.

Ishiguro, Y., Kikuchi, T., Etsuki, H., Niimi, Y., Goto, T., Morita, S., Irie, T., 2003. Does xenon anesthesia inhibit cholinesterase? An in vitro radiometric assessment. Anesthesiology 98, 791–2

Ishikawa, M., Zhang, J.H., Nanda, A., Granger, D.N., 2004. Inflammatory responses to ischemia and reperfusion in the cerebral microcirculation. Front Biosci 9, 1339-47.

Jawad, N., Rizvi, M., Gu, J., Adeyi, O., Tao, G., Maze, M., Ma, D., 2009. Neuroprotection (and lack of neuroprotection) afforded by a series of noble gases in an *in vitro* model of neuronal injury. Neurosci Lett 460, 232–236.

Jevtovic-Todorovic, V., Todorovic, S.M., Mennerick, S., Powell, S., Dikranian, K., Benshoff, N., Zorumski, C.F., Olney, JW., 1998. Nitrous oxide (laughing gas) is a NMDA antagonist, neuroprotectant and neurotoxin. Nature Med 4, 460–3

Jevtovic-Todorovic, V., Hartman, R.E., Izumi, Y., et al., 2003. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 23, 876-82.

Jia, P., Teng, J., Zou, J., et al., 2015. Xenon protects against septic acute kidney injury via miR-21 target signaling pathway. Crit Care Med 43, e250-9.

Jordan, B.D., Wright, E.L., 2010. Xenon as an anesthetic agent. AANA J 78, 387–392.

Joyce, J.A., 2000. Xenon: anesthesia for the 21st century. AANA J 68, 259–264.

Kehl, F., Pagel, P.S., Krolikowski, J.G., Gu, W., Toller, W.G., Warltier, D.C., Kersten, J.R., 2002. Isoflurane does not produce a second window of preconditioning against myocardial infarction *in vivo*. Anesth Analg 95, 1162–8

Kelen, D., Robertson, N.J., 2010. Experimental treatments for hypoxic ischaemic encephalopathy. Early Hum Dev 86, 369–377.

Kirsch, G.E., Codina, J., Birnbaumer, L., Brown, A.M., 1990. Coupling of ATP-sensitive K+ channels to A1 receptors by G proteins in rat ventricular myocytes. Am J Physiol 259, H820–26

Ko, N.U., Achrol, A.S., Martin, A.J., Chopra, M., Saloner, D.A., Higashida, R.T., Young, W.L., 2005. Magnetic resonance perfusion tracks $^{133}$Xe cerebral blood flow changes after carotid stenting. Stroke 36, 676–678.

Kodama, M., Satoh, Y., Otsubo, Y., et al., 2011. Neonatal desflurane exposure induces more robust neuroapoptosis than do isoflurane and sevoflurane and impairs working memory. Anesthesiology 115, 979-91.

Krasowski, M.D., Harrison, N.L., 1999. General anaesthetic actions on ligand-gated ion channels. Cell Mol Life Sci 55, 1278–303

Kratzer, S., Mattusch, C., Kochs, E., Eder, M., Haseneder, R., Rammes G., 2012. Xenon attenuates hippocampal long-term potentiation by diminishing synaptic and extrasynaptic N-methyl-D-aspartate receptor currents. Anesthesiology 116, 673–682.

Kubota, M., Murakami, T., Nagano, H., Eguchi, H., Marubashi, S., Kobayashi, S., Wada, H., Tanemura, M., Dono, K.,

Nakamori, S., Sakon, M., Monden, M., Mori, M., Doki, Y., 2012. Xenon-inhalation computed tomography for noninvasive quantitative measurement of tissue blood flow in pancreatic tumor. Dig Dis Sci 57, 801–805.

Landon, C., Berthault, P., Vovelle, F., Desvaux, H., 2001. Protein Sci. 10, 762.

Lane, G.A., Nahrwold, M.L., Tait, A.R., Taylor-Busch, M., Cohen, P.J., Beaudoin AR., 1980. Anesthetics as teratogens: nitrous oxide is fetotoxic, xenon is not. Science 210, 899–901.

Langhelle, A., Nolan, J., Herlitz, J., et al., 2005. Recommended guidelines for reviewing, reporting, and conducting research on postresuscitation care: the Utstein style. Resuscitation 66, 271-83.

Latchaw, R.E., Yonas, H., Hunter, G.J., Yuh, W.T.C., Ueda, T., Sorensen, A.G., Sunshine, J.L., Biller, J., Wechsler, L., Higashida, R., Hademenos, G., 2003. Guidelines and recommendations for perfusion imaging in cerebral ischemia a scientific statement for healthcare professionals by the writing group on perfusion imaging, from the council on cardiovascular radiology of the American heart association. Stroke 34, 1084.

Lawrence, J.H., Loomis, W.F., Tobias, C.A., Turpin, F.H., 1946. Preliminary observations on the narcotic effect of xenon with a review of values for solubilities of gases in water and oils. J Physiol 105, 197-204.

Li, D., Huang, B., Liu, J., Li, L., Li, X., 2013. Decreased brain K(ATP) channel contributes to exacerbating ischemic brain injury and the failure of neuroprotection by sevoflurane post-conditioning in diabetic rats. PLoS One 8, e73334.

Liu, W., Khatibi, N., Sridharan, A., Zhang, J.H., 2011. Application of medical gases in the field of neurobiology. Med Gas Res 1, 13.

Liu, W., Liu, Y., Chen, H., Liu, K., Tao, H., Sun, X., 2013. Medical Gas Research 3, 3.

Lockwood, G.G., Franks, N.P., Downie, N.A., Taylor, K.M., Maze, M., 2006. Feasibility and safety of delivering xenon to patients undergoing coronary artery bypass graft surgery while on cardiopulmonary bypass: phase I study. Anesthesiology 104, 458-65.

Lopez, M.M., Kosk-Kosicka, D., 1995. How do volatile anesthetics inhibit Ca2+-ATPases? J Biol Chem 270, 28239–28245.

Luo, Y., Ma, D., Ieong, E., Sanders, R.D., Yu, B., Hossain, M., Maze, M., 2008. Xenon and sevoflurane protect against brain injury in a neonatal asphyxia model. Anesthesiology 109, 782–789.

Lutz, M.R., Liu, H., 2004. Sevoflurane produces a delayed window of protection in young rat myocardium and fails to in aged rat myocardium (abstract). Anesthesiology 101(suppl), A-732

Lynch, C. 3rd., Baum, J., Tenbrinck, R., 2000. Xenon anesthesia. Anesthesiology 92, 865–868.

Lynch, D.R., Guttmann, R.P., 2002. Excitotoxicity: perspectives based on N-methyl-D-aspartate receptor subtypes. J Pharmacol Exp Ther 300, 717-23.

Ma, D., Wilhelm, S., Maze, M., Franks, N.P., 2002. Neuroprotective and neurotoxic properties of the ‘inert’ gas, xenon. Br J Anaesth 89, 739-46.

Ma, D., Yang, H., Lynch, J., Franks, N.P., Maze, M., Grocott, H.P., 2003a. Xenon attenuates cardiopulmonary bypass-induced neurologic and neurocognitive dysfunction in the rat. Anesthesiology 98, 690–8

Ma, D., Hossain, M., Rajakumaraswamy, N., Franks, N.P., Maze, M., 2003b. Combination of xenon and isoflurane produces a synergistic protective effect against oxygenglucose deprivation injury in a neuronal-glial co-culture model. Anesthesiology 99, 748–51

Ma, D., Hossain, M., Chow, A., et al., 2005. Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia. Ann Neurol 58, 182-93.

Ma, D., Hossain, M., Pettet, G.K.J., Luo, Y., Lim, T., Akimov, S., Sanders, R.D., Franks, N.P., Maze, M., 2006. Xenon preconditioning reduces brain damage from neonatal asphyxia in rats. J Cereb Blood Flow Metab 26, 199–208

Ma, D., Williamson, P., Januszewski, A., et al., 2007. Xenon mitigates isoflurane-induced neuronal apoptosis in the developing rodent brain. Anesthesiology 106, 746-53.

Ma, D., Lim, T., Xu, J., et al., 2009. Xenon preconditioning protects against renal ischemic-reperfusion injury via HIF-1alpha activation. J Am Soc Nephrol 20, 713-20.

Marcucci, C., Leopold, D.A., Cullen, M., Zinreich, S.J., Simon, B.A., 2001. Dynamic assessment of paranasal sinus ventilation using xenon enhanced computed tomography. Ann Otol Rhinol Laryngol 110, 968-75.

Marin, R., 2001. Plasma TV: That New Object of Desire. The New York Times, Style Section.

Marshall, D.B., Strohbusch, F., Eyring, E.M., 1981. J. Chem. Engng. Data 26, 333.

Martin, J.L., Ma, D., Hossain, M., Xu, J., Sanders, R.D., Franks, N.P., Maze, M., 2007. Asynchronous administration of xenon and hypothermia significantly reduces brain infarction in the neonatal rat. Br J Anaesth 98, 236–240.

Marx, T., Schmidt, M., Schirmer, U., Reinelt, H., 2000. Xenon anaesthesia. J R Soc Med 93, 513–517.

Maze, M., 2016. Preclinical neuroprotective actions of xenon and possible implications for human therapeutics: a narrative review. Can. J Aneth. 63, 212-26.

McKim, S., Hinton, J.F., 1994. Biochim. Biophys. Acta 1193, 186.

Merelli, A., Czornyj, L., Lazarowski, A., 2013. Erythropoietin: a neuroprotective agent in cerebral hypoxia, neurodegeneration, and epilepsy. Curr Pharm Des 19, 6791-801.

Miller, S.P., Weiss, J., Barnwell, A., et al., 2002. Seizure-associated brain injury in term newborns with perinatal asphyxia. Neurology 58, 542-8.

Miyazaki, Y., Adachi, T., Utsumi, J., Shichino, T., Segawa, H., 1999. Xenon has greater inhibitory effects on spinal dorsal horn neurons than nitrous oxide in spinal cord transected cats. Anesth Analg 88, 893–7

Mori, T., Zhao, X., Zuo, Y., Aistrup, G.L., Nishikawa, K., Marszalec, W., Yeh, J.Z., Narahashi, T., 2001. Modulation of neuronal nicotinic acetylcholine receptors by halothane in rat cortical neurons. Mol Pharmacol 59, 732–43

Mountz, J.M., Liu, H.G., Deutsch, G., 2003. Neuroimaging in cerebrovascular disorders:

measurement of cerebral physiology after stroke and assessment of stroke recovery. Semin Nucl Med 33, 56–76.

Mu¨llenheim, J., Ebel, D., Fra¨ßdorf, J., Preckel, B., Tha¨mer, V., Schlack, W., 2002. Isoflurane preconditions myocardium against infarction *via* release of free radicals. Anesthesiology 96, 934–40

Mu¨llenheim, J., Ebel, D., Bauer, M., Otto, F., Heinen, A., Fra¨ßdorf, J., Preckel, B., Schlack, W., 2003. Sevoflurane confers additional cardioprotection after ischemic late preconditioning in rabbits. Anesthesiology 99, 624–31

Nagata, A., Nakao, Si S., Nishizawa, N., et al., 2001. Xenon inhibits but N(2)O enhances ketamine-induced c-Fos expression in the rat posterior cingulate and retrosplenial cortices. Anes Analg 92, 362-8.

Nagele, P., Metz, L.B., Crowder, C.M., 2004. Nitrous oxide (N2O) requires the Nmethyl- D-aspartate receptor for its action in Caenorhabditis elegans. Proc Natl Acad Sci U S A 101, 8791–6

Nagele, P., Metz, L.B., Crowder, C.M., 2005. Xenon acts by inhibition of non–Nmethyl- D-aspartate receptor mediated glutamatergic neurotransmission in Caenorhabditis elegans. Anesthesiology 103, 508–13

Natale, G., Cattano, D., Abramo, A., Forfori, F., Fulceri, F., Fornai, F., Paparelli, A., Giunta, F., 2006. Morphological evidence that xenon neuroprotects against N-methyl-DL-aspartic acid-induced damage in the rat arcuate nucleus: a time-dependent study. Ann N Y Acad Sci 1074, 650–658.

Newman, M.F., Kirchner, J.L., Phillips-Bute, B., et al., 2001. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 344, 395-402.

Nicoll, R.A., Madison, D.V., 1982. General anesthetics hyperpolarize neurons in the vertebrate central nervous system. Science 217, 1055–7

Nisticò, S.P., Saraceno, R., Capriotti, E., Felice, C.D., Chimenti, S., 2008. Efficacy of monochromatic excimer light (308 nm) in the treatment of atopic dermatitis in adults and children. Photomed Laser Surg 26, 14–18.

Olney, J.W., 1969. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. Science 164, 719-21.

Pagel, P,S., 2010. Cardioprotection by noble gases. J Cardiothorac Vasc Anesth 24, 143–163.

Parsons, C.G., Gruner, R., Rozental, J., Millar, J., Lodge, D., 1993. Patch clamp studies on the kinetics and selectivity of N-methyl-Daspartate receptor antagonism by memantine (1-amino-3,5dimethyladamantan).
Neuropharmacology 32, 1337-50.

Parsons, M.W., Li, T., Barber, P.A., Yang, Q., Darby, D.G., Desmond, P.M., Gerraty, R.P., Tress, B.M., Davis, S.M., 2000. Combined (1)H MR spectroscopy and diffusion weighted MRI improves the prediction of stroke outcome. Neurology 55, 498–505.

Patel C.K., Bennett, W.R. Jr., Faust, W.L., McFarlane, R.A., 1962. Infrared spectroscopy using stimulated emission techniques. Phys Rev. Lett. 9, 102-4.

Patel, A.J., Honore, E., 2001. Properties and modulation of mammalian 2P domain K+ channels. Trends Neurosci 24, 339–46

Paule, M.G., Li, M., Allen, R.R., et al., 2011. Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys. Neurotoxicol Teratol 33, 220-30.

Penniston, J.T., Enyedi, A., 1994. Plasma membrane Ca2+ pump: Recent developments. Cell Physiol Biochem 4, 148–59

Perlman, J.M., Wyllie, J., Kattwinkel, J., et al., 2010. Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 122, S516-38.

Petzelt, C., Ose´s-Prieto, J., Klett, F.F., Schmehl, W., Kox, W.J., 1997. Effects of xenon on intracellular Ca2+ release in human endothelial cells. Exp Biol Online 2, 3–9

Petzelt, C., Taschenberger, G., Schmehl, W., Hafner, M., Kox, W.J., 1999a. Xenon induces metaphase arrest in rat astrocytes. Life Sci 65, 901–13

Petzelt, C., Taschenberger, G., Schmehl, W., Kox, W.J., 1999b. Xenon-induced inhibition of Ca2+-regulated transitions in the cell cycle of human endothelial cells. Pflugers Arch 437, 737–44

Petzelt, C., Blom, P., Schmehl, W., Muller, J., Kox, W.J., 2003. Prevention of neurotoxicity in hypoxic cortical neurons by the noble gas xenon. Life Sci 72, 1909-18.

Petzelt, C., Blom, P., Schmehl, W., Mueller, J., Kox, W.J., 2004. Xenon prevents cellular damage in differentiated PC-12 cells exposed to hypoxia. BMC Neurosci 5, 55

Pfeffer, M.A., Burdmann, E.A., Chen, C.Y., et al., 2009. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 361, 2019-32.

Plested, A.J., Wildman, S.S., Lieb, W.R., Franks, N.P., 2004. Determinants of the Sensitivity of AMPA Receptors to Xenon. Anesthesiology 100, 347–358.

Prange, T., Schiltz, M., Pernot, L., Colloc'h, N., Longhi, S., Bourguet, W., Fourme, R., 1998. Exploring hydrophobic sites in proteins with xenon or krypton. Proteins 30, 61–73.

Preckel, B., Müllenheim, J., Moloschavij, A., Thämer, V., Schlack, W., 2000. Xenon administration during early reperfusion reduces infarct size after regional ischemia in the rabbit heart in vivo. Anesth Analg 91, 1327–1332.

Preckel, B., Schlack, W., Heibel, T., Rütten, H., 2002. Xenon produces minimal haemodynamic effects in rabbits with chronically compromised left ventricular function. Br J Anaesth 88, 264–269.

Preckel, B., Weber, N.C., Sanders, R.D., Maze, M., Schlack, W., 2006. Molecular mechanisms transducing the anesthetic, analgesic, and organ-protective actions of xenon. Anesthesiology 105, 187–197.

Qu, Y.Y., Yuan, M.Y., Liu, Y., Xiao, X.J., Zhu, Y.L., 2015. The protective effect of epoxyeicosatrienoic acids on cerebral ischemia/reperfusion injury is associated with PI3K/Akt pathway and ATP-sensitive potassium channels. Neurochem Res 40, 1-14.

Quillin, M.L., Breyer, W.A., Griswold, I.J., Matthews, B.W., 2000. J. Mol. Biol. 302, 955.

Rajakumaraswamy, N., Ma, D., Hossain, M., Sanders, R.D., Franks, N.P., Maze, M., 2006. Neuroprotective interaction produced

by xenon and dexmedetomidine on in vitro and in vivo neuronal injury models. Neurosci Lett 409, 128–133.

Reinelt, H., Schirmer, U., Marx, T., Topalidis, P., Schmidt, M., 2001. Diffusion of xenon and nitrous oxide into the bowel. Anesthesiology 94, 475-7

Reinelt, H., Marx, T., Kotzerke, J., Topalidis, P., Luederwald, S., Armbruster, S., Schirmer, U., Schmidt, M., 2002. Hepatic function during xenon anesthesia in pigs. Acta Anaesthesiol Scand 46, 713–716.

Rentzepis, P.M., Douglass, D.C., 1981. Nature 293, 165.

Rizvi, M., Jawad, N., Li, Y., Vizcaychipi, M.P., Maze, M., Ma, D., 2010. Effect of noble gases on oxygen and glucose deprived injury in human tubular kidney cells. Exp Biol Med 235, 886–891.

Rossaint, R., Reyle-Hahn, M., Schulte, Am.Esch.J., Scholz, J., Scherpereel, P., Vallet, B., Giunta, F., Del Turco, M., Erdmann, W., Tenbrinck, R., Hammerle, A.F., Nagele., 2003. Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. Anesthesiology 98, 6–13.

Sabir, H., Bishop, S., Cohen, N., et al., 2013. Neither xenon nor fentanyl induces neuroapoptosis in the newborn pig brain. Anesthesiology 119, 345-57.

Saha, G., Macintyre, W., Go, R., 1994. Radiopharmaceuticals for brain imaging. Semin Nucl Med 24, 324–349.

Sakamoto, S., Nakao, S., Masuzawa, M., et al., 2006. The differential effects of nitrous oxide and xenon on extracellular dopamine levels in the rat nucleus accumbens: a microdialysis study. Anesth Analg 103, 1459-63.

Sanders, R., Franks, N., Maze, M., 2003. Xenon: no stranger to anaesthesia. Br. J. Anaesth. 91, 709–717.

Sanders, R.D., Ma, D., Maze, M., 2004. Xenon: elemental anaesthesia in clinical practice. Br Med Bull 71, 115–135.

Sanders, R.D., Maze, M., 2005. Xenon: from stranger to guardian. Curr Opin Anaesthesiol 18, 405–411.

Satomoto, M., Satoh, Y., Terui, K., et al., 2009. Neonatal exposure to sevoflurane induces abnormal social behaviors and deficits in fear conditioning in mice. Anesthesiology 110, 628-37.

Saver, J.L., Starkman, S., Eckstein, M., et al., 2015. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. N Engl J Med 372, 528-36.

Schiltz, M., Fourme, R., Broutin, I., Prange, T., 1995. The catalytic site of serine proteinases as a specific binding cavity for xenon. Structure 3, 309–16.

Schiltz, M., Prange, T., Fourme, R., 1994. J. Appl. Cryst. 27, 950.

Schmidt, M., Marx, T., Glöggl, E., Reinelt, H., Schirmer, U., 2005. Xenon attenuates cerebral damage after ischemia in pigs. Anesthesiology 102, 929–936.

Schoenborn, B.P., Watson, H.C., Kendrew, J.C., 1965. Nature 207, 28.

Schubert, H., Eiselt, M., Walter, B., Fritz, H., Brodhun, M., Bauer, R., 2012. Isoflurane/nitrous oxide anesthesia and stress-induced procedures enhance neuroapoptosis in intrauterine growthrestricted piglets. Intensive Care Med 38, 1205-14.

Sheng, S.P., Lei, B., James, M.L., et al., 2012. Xenon neuroprotection in experimental stroke: interactions with

hypothermia and intracerebral hemorrhage. Anesthesiology 117, 1262-75.

Shichino, T., Murakawa, M., Adachi, T., Miyazaki, Y., Segawa, H., Fukuda, K., Mori, K., 2002. Effects of xenon on acetylcholine release in the rat cerebral cortex in vivo. Br J Anaesth 88, 866–8

Shu, Y., et al., 2010. Xenon pretreatment attenuates anesthetic-induced apoptosis in the developing brain in comparison with nitrous oxide and hypoxia. Anesthesiology 113, 360–368.

Shuaibov, A.K., Shimon, L.L., Grabovaya, A., 2003. A xenon-iodine electric discharge bactericidal lamp. Tech. Phys. Lett. 29, 871-2.

Singh, G., Janicki, P.K., Horn, J.-L., Janson, V.E., Franks, J.J., 1995. Inhibition of plasma membrane Ca2+-ATPase pump activity in cultured C6 glioma cells by halothane and xenon. Life Sci 56, PL219–24

Smith, W.S., 2004. Pathophysiology of focal cerebral ischemia: a therapeutic perspective. J Vasc Interv Radiol 15, S3–S12.

Smul, T., Stumpner, J., Lange, M., Roewer, N., Kehl, F., 2005. Desflurane induces a 1st and 2nd window of preconditioning against myocardial infarction. FASEB J 19, A691–386.12

Soltis, S.M., Stowell, M.H.B., Wiener, M.C., Phillips, G.N., Rees, D.C., 1997. J. Appl. Cryst. 30, 190.

Spahr-Schopfer, I., Vutskits, L., Toni, N., Buchs, P.A., Parisi, L., Muller, D., 2000. Differential neurotoxic effects of propofol on dissociated cortical cells and organotypic hippocampal cultures. Anesthesiology 92, 1408-17.

Speechly-Dick, M.E., Grover, G.J., Yellon, D.M., 1995. Does ischemic preconditioning in the human involve protein kinase C and the ATP-dependent K+ channel? Studies of contractile function after simulated ischemia in an atrial *in vitro* model. Circ Res 77, 1030–5

Spence, M.M., Rubin, S.M., Dimitrov, I.E., Ruiz, E.J., Wemmer, D.E., Pines, A., Yao, S.Q., Tian, F., Schultz, P.G., 2001. Proc. Natl Acad. Sci. USA 98, 10654.

Spieth, P.M., Parotto, M., 2011. Xenon and the developing brain. Minerva Anestesiol 77, 565–566.

Sprung, J., Abdelmalak, B., Gottlieb, A., Mayhew, C., Hammel, J., Levy, P.J., O'Hara, P., Hertzer, NR., 2000. Analysis of risk factors for myocardial infarction and cardiac mortality after major vascular surgery. Anesthesiology 93, 129–140.

Sprung, J., Flick, R.P., Katusic, S.K., et al., 2012. Attention-deficit/ hyperactivity disorder after early exposure to procedures requiring general anesthesia. Mayo Clin Proc 87, 120-9.

Sun, H.S., Xu, B., Chen, W., et al., 2015. Neuronal K(ATP) channels mediate hypoxic preconditioning and reduce subsequent neonatal hypoxic-ischemic brain injury. Exp Neurol 263, 161-71.

Suzuki, T., Koyama, H., Sugimoto, M., Uchida, I., Mashimo, T., 2002. The diverse actions of volatile and gaseous anesthetics on human-cloned 5-hydroxytryptamine3 receptors expressed in Xenopus oocytes. Anesthesiology 96, 699-704.

Suzuki, T., Ueta, K., Sugimoto, M., Uchida, I., Mashimo, T., 2003. Nitrous oxide and xenon inhibit the human (a7)5 nicotinic acetylcholine receptor expressed in xenopus oocyte. Anesth Analg 96, 443–8

Takahashi, T., Ueno, H., Shibuya, M., 1999. VEGF activates protein kinase C-dependent, but Ras-independent Raf-MEK-MAP kinase pathway for DNA synthesis in primary endothelial cells. Oncogene 18, 2221–30

Thoresen, M., Hobbs, C.E., Wood, T., Chakkarapani, E., Dingley, J., 2009. Cooling combined with immediate or delayed xenon inhalation provides equivalent long-term neuroprotection after neonatal hypoxia-ischemia. J Cereb Blood Flow Metab 29, 707–714.

Tilton, R.F., Kuntz, I.D., 1982. Biochemistry 21, 6850.

Tooley, J.R., Satas, S., Porter, H., Silver, I.A., Thoresen, M., 2003. Head cooling with mild systemic hypothermia in anesthetized piglets is neuroprotective. Ann Neurol 53, 65–72.

Tonner, P.H., 2006. Xenon: one small step for anaesthesia. . . ? Curr Opin Anaesthesiol 19, 382–384.

Trudell, J.R., Koblin, D.D., Eger, E.I., 1998. Anesth. Analg. 87, 411.

Twaroski, D.M., Yan, Y., Olson, J.M., Bosnjak, Z.J., Bai, X., 2014. Downregulation of microRNA-21 is involved in the propofol-induced neurotoxicity observed in human stem cell-derived neurons. Anesthesiology 121, 786-800.

Uecker, M., Da Silva, R., Grampp, T., Pasch, T., Schaub, M.C., Zaugg, M., 2003. Translocation of protein kinase C isoforms to subcellular targets in ischemic and anesthetic preconditioning. Anesthesiology 99, 138–47

Utsumi, J., Adachi, T., Miyazaki, Y., Kurata, J., Shibata, M., Murakawa, M., Arai, T., Mori K., 1997. The effect of xenon on spinal dorsal horn neurons: A comparison with nitrous oxide. Anesth Analg 84, 1372–6

Vizcaychipi, M.P., Lloyd, D.G., Wan, Y., Palazzo, M.G., Maze, M., Ma, D., 2011. Xenon pretreatment may prevent early memory decline after isoflurane anesthesia and surgery in mice. PLoS One 6, e26394.

Wakeno-Takahashi, M., Otani, H., Nakao, S., Imamura, H., Shingu, K., 2005. Isoflurane induces second window of preconditioning through upregulation of inducible nitric oxide synthase in the rat heart. Am J Physiol Heart Circ Physiol 289, H2585–91

Weber, N.C., Toma, O., Wolter, J.I., Obal, D., Mu¨llenheim, J., Preckel, B., Schlack, W., 2005a. The noble gas xenon induces pharmacological preconditioning in the rat heart *in vivo via* induction of PKC-e and p38 MAPK. Br J Pharmacol 144, 123–32

Weber, N.C., Toma, O., Wolter, J.I., Wirthle, N.M., Schlack, W., Preckel, B., 2005b. Mechanisms of xenon and isoflurane induced preconditioning: A potential link to the cytoskeleton *via* the MAPKAPK-2/HSP27 pathway. Br J Pharmacol 146, 445–55

Weber, N.C., Toma, O., Stursberg, J., Schlack, W., Preckel, B., 2005c. Mechanisms of xenon induced preconditioning: Xenon differently regulates p44/42 MAPK (ERK1/2) and p54/46 MAPK (JNK1/2) (abstract). Anesthesiology 103(suppl), A-491

Weinbrenner, C., Liu, G.S., Cohen, M.V., Downey, J.M., 1997. Phosphorylation of Tyrosine 182 of p38 mitogen activated protein kinase correlates with the protection

of preconditioning in the rabbit heart. J Mol Cell Cardiol 29, 2383–91

Wilhelm, S., Ma, D., Maze, M., Franks, N.P., 2002. Effects of xenon on in vitro and in vivo models of neuronal injury. Anesthesiology 96, 1485-91.

Williamson, P.B., Ma, D., Hossain, M., Franks, N.P., Maze, M., 2004. Xenon does not cause apoptotic neurodegeneration in the neonatal rat, and protects against isoflurane-induced apoptosis (abstract). Anesthesiology 101, A-864

Wintermark, M., Sesay, M., Barbier, E., Borbély, K., Dillon, W.P., Eastwood, J.D., Glenn, T.C., Grandin, C.B., Pedraza, S., Soustiel, J.-F., Nariai, T., Zaharchuk, G., Caillé, J.-M., Dousset, V., Yonas, H., 2005. Comparative overview of brain perfusion imaging techniques. Stroke 36, e83–e99.

Wirthle, N.M., Weber, N.C., Wolter, J.I., Toma, O., Schlack, W., Preckel, B., 2005. Xenon preconditioning induces isoform-specific activation of protein kinase C in the rat heart. Ana¨sthesiologie und Intensivmedizin 12-2, 196–7

Wise-Faberowski, L., Zhang, H., Ing, R., Pearlstein, R.D., Warner, D.S., 2005. Isoflurane-induced neuronal degeneration: an evaluation in organotypic hippocampal slice cultures. Anesth Analg 101, 651-7.

Wishnia, A., 1969. Biochemistry 8, 5064.

Wu, Y.W., Bauer, L.A., Ballard, R.A., et al., 2012. Erythropoietin for neuroprotection in neonatal encephalopathy: safety and pharmacokinetics. Pediatrics 130, 683-91.

Xu, Y., Tang, P., 1997. Amphiphilic sites for general anesthetic action? Evidence from 129Xe-[1H] intermolecular nuclear Overhauser effects. Biochim Biophys Acta 1323, 154–162.

Yamakura, T., Harris, R.A., 2000. Effects of gaseous anesthetics nitrous oxide and xenon on ligand-gated ion channels: Comparison with isoflurane and ethanol. Anesthesiology 93, 1095–101

Yamamoto, H., Takata, M., Merczin, N., Franks, N.P., Maze, M., 2003. Xenon's effect on adhesion molecule expression in inflammation model of mouse brain endothelial cell (abstract). Anesthesiology 99, A-477

Yang, X.M., Sato, H., Downey, J.M., Cohen, M.V., 1997. Protection of ischemic preconditioning is dependent upon a critical timing sequence of protein kinase C activation. J Mol Cell Cardiol 29, 991–9

Yang, T., et al., 2012. Xenon and sevoflurane provide analgesia during labor and fetal brain protection in a perinatal rat model of hypoxia–ischemia. PLoS ONE 7, e37020.

Yon, J.H., Daniel-Johnson, J., Carter, L.B., Jevtovic-Todorovic, V., 2005. Anesthesia induces neuronal cell death in the developing rat brain via the intrinsic and extrinsic apoptotic pathways. Neuroscience 135, 815-27.

Yoshida, H., Kushikata, T., Kubota, T., Hirota, K., Ishihara, H., Matsuki, A., 2001. Xenon inhalation increases norepinephrine release from the anterior and posterior hypothalamus in rats. Can J Anesth 48, 651–5

Young, C., Tenkova, T., Dikranian, K., Olney, J.W., 2004. Excitotoxic versus apoptotic mechanisms of neuronal cell death in perinatal hypoxia/ischemia. Curr Mol Med 4, 77-85.

Zhao, H., Watts, H.R., Chong, M., et al., 2013. Xenon treatment protects against cold

ischemia associated delayed graft function and prolongs graft survival in rats. Am J Transplant 13, 200618.

Zhao, H., Huang, H., Ologunde, R., et al., 2015. Xenon treatment protects against remote lung injury after kidney transplantation in rats. Anesthesiology 122, 1312-26.

Zhuang, L., Yang, T., Zhao, H., et al., 2012. The protective profile of argon, helium, and xenon in a model of neonatal asphyxia in rats. Crit Care Med 40, 1724-30.

Zou, X., Liu, F., Zhang, X., et al., 2011. Inhalation anesthetic-induced neuronal damage in the developing rhesus monkey. Neurotoxicol Teratol 33, 592-7.