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Neuroprotection and neurotoxicity in the developing brain: an update on the effects of dexmedetomidine and xenon

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ABSTRACT

Growing and consistent preclinical evidence, combined with early clinical epidemiological observations, suggest potentially neurotoxic effects of commonly used anesthetic agents in the developing brain. This has prompted the FDA to issue a safety warning for all sedatives and anesthetics approved for use in children under three years of age. Recent studies have identified dexmedetomidine, the potent α2-adrenoceptor agonist, and xenon, the noble gas, as effective anesthetic adjuvants that are both less neurotoxic to the developing brain, and also possess neuroprotective properties in neonatal and other settings of acute ongoing neurologic injury. Dexmedetomidine and xenon are effective anesthetic adjuvants that appear to be less neurotoxic than other existing agents and have the potential to be neuroprotective in the neonatal and pediatric settings. Although results from recent clinical trials and case reports have indicated the neuroprotective potential of xenon and dexmedetomidine, additional randomized clinical trials corroborating these studies are necessary. By reviewing both the existing preclinical and clinical evidence on the neuroprotective effects of dexmedetomidine and xenon, we hope to provide insight into the potential clinical efficacy of these agents in the management of pediatric surgical patients.

1. Introduction

There has been a 30% increase in surgical procedures over the past 10 years (Health and Social Care Information Centre, 2015), whilst young patients represent 10% of overall surgeries (DeFrances et al., 2007). This demonstrates the growing demand for surgery and the consequential need for safe and effect anesthetic agents. A steady increase in reproducible and preclinical evidence in rodents and nonhuman primates suggest that certain anesthetic agents may have neurotoxic effects in the developing brain and precipitate significant cognitive sequelae. Epidemiological evidence has been less consistent, but appears to indicate that neurotoxicity may ensue following prolonged and/or repeated exposures to general anesthetics early in life, prompting the U.S. Food and Drug Administration (FDA) to issue such a warning (U.S. Food and Drug Administration, 2016). Exposure of neonatal rats to a conventional anesthetic regimen of isoflurane, nitrous oxide and midazolam has been shown to produce a 50-fold increase in neuronal degeneration within the laterodorsal and anteroventral thalamic nuclei (Jevtovic-Todorovic et al., 2003). As a result, safe, anesthetic-sparing agents that are also neuroprotective have been widely investigated in order to avoid the deleterious neurological effects of conventional anesthetics. In this review, we discuss two such anesthetic-sparing agents that have demonstrated neuroprotective effects in preclinical studies, and may be used in concert to limit the potential for anesthetic-induced neurotoxicity.

The potent α_2-adrenoceptor agonist, dexmedetomidine, has sedative, analgesic, sympatholytic and anxiolytic properties, enabling its safe and effective use as an anesthetic adjunct in the perioperative setting. The "cooperative sedation" that dexmedetomidine induces, whereby patients appear to be asleep but can still be easily roused, is distinctive and unique. Preclinical and epidemiological studies have also demonstrated that dexmedetomidine possesses significant neuroprotective properties, which are discussed in further detail below.

Xenon is a chemically non-reactive, noble mono-atomic gas present in very small amounts (88 parts per billion) in the atmosphere. Similar to nitrous oxide (N_2O) and ketamine, xenon is an antagonist of the NMDA subtype of glutamate receptors (Jawad et al., 2009; Laitio et al., 2016). While NMDA antagonists can produce neuroprotection, xenon does not exhibit the psychotomimetic properties that are usually present in this subclass of molecules. Xenon is devoid of two other features that are present in these other NMDA antagonist anesthetics; namely,

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neurotoxicity and adverse hemodynamic properties (Wilhelm et al., 2002).

This review evaluates recent preclinical and clinical evidence for the neurotoxic and neuroprotective effects of dexmedetomidine and xenon, with emphasis on pediatric surgical patients.

2. Molecular sites of action

2.1. Dexmedetomidine

Dexmedetomidine is primarily an α2-adrenoceptor agonist. However, as an imidazole derivative, it also operates on imidazoline 'I' receptors (Savola & Savola, 1996). Approved in 1999 by the FDA as a short-term sedative and analgesic for intubated patients in intensive care settings, it was also eventually approved in 2008 for use in non-intubated patients and perioperative care. Dexmedetomidine has also caught the attention of researchers and clinicians due to its cardioprotective, renoprotective, and neuroprotective properties in preclinical studies (Pagel, 2010; Weber et al., 2005; Jia et al., 2015; Ma et al., 2009; Banks et al., 2010).

2.1.1. Alpha-2 adrenoceptor

Adrenergic receptors (or adrenoceptors) were originally categorized into α and β receptors based on their response to natural and synthetic catecholamines (Ahlquist, 1948; Langer, 1974). The α adrenoceptors are located both pre- and postsynaptically, with the former being responsible for regulation of neurotransmitter release (Langer, 1974). The α-2 adrenoceptor is a transmembrane receptor that mediates its effects *via* the activation of guanine-nucleotide regulatory binding proteins (G proteins) (Fig. 1). At least three different α-2 isoreceptors (α-2A, α-2B and α-2C), with ~70% homology, have been identified based on pharmacological and molecular biological probes (Coursin et al., 2001). The α-2 adrenoceptors mediate a variety of physiological effects (sedation and analgesia, platelet aggregation, peripheral venoconstriction, decreased salivation, gastric motility and pancreatic release of insulin, increased glomerular filtration rate, decrease in intraocular pressure) due to their presence in the peripheral and central nervous systems, platelets and various organs, including the kidney, liver, pancreas and eye (Metz et al., 1978) (Fig. 1). Clinically used α-2 agonists include dexmedetomidine (for perioperative use), brimonidine (for glaucoma), clonidine and moxonidine (for blood pressure control) (Kallio et al., 1989; Fairbanks et al., 2009; Bylund et al., 1994).

Using more selective compounds permits more focused responses (Lakhlani et al., 1997; Maze et al., 2001; Hoefke & Kobinger, 1966; MacMillan et al., 1996; Knaus et al., 2007; Kamibayashi & Maze, 2000). The α-2A subtype promotes sedation, analgesia, hypnosis, neuroprotection and sympatholysis. The α-2B receptor subtype mediates suppression of shivering centrally, promotes analgesia by acting on spinal cord sites and causes peripheral vasoconstriction. The α-2C subtype is associated with adrenaline outflow regulation from the adrenal medulla, mediation of cognitive sensory processing and mood and stimulant-induced locomotor activity. Presynaptic inhibition of neurotransmitter release is transduced by all three receptor subtypes (Panzer et al., 2009). The relative selectivity of dexmedetomidine for the α-2A receptor subtype, which is primarily responsible for sedation, provides for a more effective sedative and analgesic agent compared to clonidine (MacDonald et al., 1997); α-2A receptor agonism is exclusively responsible for the neuroprotective effects of dexmedetomidine (Virtanen et al., 1988; Ma et al., 2004a).

2.1.2. Post-receptor effector mechanisms

Sedation and analgesia are the two primary clinical effects that dexmedetomidine elicits in order to safely and effectively manage patients perioperatively.

2.1.2.1. Hypnosis and sedation. The locus coeruleus (LC) is the major noradrenergic nucleus in the brain, located in the pons, and the inhibition of its firing through membrane hyperpolarization is responsible for sedation by disinhibiting the ventrolateral preoptic nucleus (VLPO), the so-called 'sleep switch' (Birnbaumer et al., 1990; Correa-Sales et al., 1992; Nacif-Coelho et al., 1994).

2.1.2.2. Analgesia. Dexmedetomidine is able to modulate nociceptive transmission in the CNS by acting on both supraspinal and spinal sites. Activation of α-2 adrenoceptors in the dorsal horn of the spinal cord

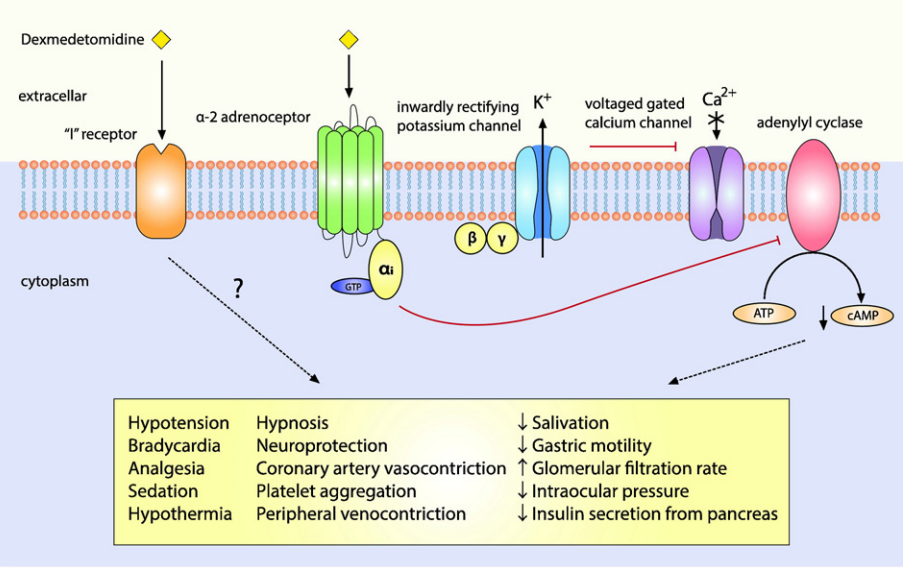

Fig. 1. The mechanism of action of dexmedetomidine. Dexmedetomidine is an agonist of the α-2 adrenoceptor, a transmembrane G-protein coupled receptor. Activation of the α-2 adrenoceptor inhibits adenylyl cyclase, which causes an intracellular decrease of cAMP. This leads to a series of cellular events and many systemic effects, as listed above. Agonism of the α-2 adrenoceptor also causes an activation of the inwardly rectifying potassium channel, leading to an efflux of K^+ and inhibition of voltage-gated Ca^{2+} channels. This causes membrane hyperpolarization, such as hyperpolarization of the neuronal membrane in the locus coeruleus (LC), which suppresses neuronal firing and ascending noradrenergic activity. Dexmedetomidine also binds to the "I" receptor, which may also be responsible for some of the actions listed above. ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; GTP, guanosine triphosphate; I receptor, imidazoline receptor.

inhibits release of neurotransmitters, preventing propagation of neural activity in nociceptive pathways (Kuraishi et al., 1985).

2.1.3. "I" receptor

Chemically, dexmedetomidine is an imidazoline compound (due to the presence of an imidazole ring) and interacts with imidazoline or "I" receptors, which may be responsible for some of the effects of dexmedetomidine (Kamibayashi & Maze, 2000; Maze & Tranquilli, 1991; Khan et al., 1999). Ligation of the imidazoline I_2 receptor, with administration of either imidazoline agonists or antagonists, protects neurons against ischemic injury (Maiese et al., 1992).

2.1.4. No direct GABAmimetic action

Dexmedetomidine promotes sedation in a manner very similar to physiological sleep due to its regulation of wakefulness *via* its action on the VLPO neuronal circuity (Nelson et al., 2003; Fernandes et al., 2016). Most other sedative-hypnotic agents act downstream of VLPO, directly on $GABA_A$ receptors.

2.1.5. Effects at the NMDA receptor

Although dexmedetomidine lacks affinity for the NMDA subtype of the glutamate receptor, it can affect NMDA-mediated processes by decreasing the presynaptic release of glutamate and inducing postsynaptic hyperpolarization, thereby limiting NMDA-mediated long-term potentiation (Zhou et al., 2015). Dexmedetomidine also prevents upregulation of the NR2B subunit of the NMDA receptor, thus ameliorating the learning and memory impairment that occurs after electroconvulsive therapy (Gao et al., 2016).

2.2. Xenon

Xenon was discovered by Ramsay in 1898 using fractional distillation of liquefied air (Joyce, 2000). Initial studies to prevent dysphoria in deep-sea divers led to the use of xenon as an anesthetic (Marx et al., 2000). In recent years, xenon has been noted to have neuroprotective properties (Fries et al., 2008; Parsons et al., 2000; Liu et al., 2011; Tonner, 2006; Homi et al., 2003; Ma et al., 2002). It is likely that xenon exerts its anesthetic and neuroprotective effects by competing for the glycine co-activation site on the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor subtype (Fries et al., 2008; Chakkarapani et al., 2009; Natale et al., 2006) (Fig. 2). Xenon does not share the psychotomimetic and neurotoxic properties of other anesthetics of the NMDA antagonist subclass, possibly because its antagonistic action is not due to blockade of the ion pore (Franks et al., 1998).

2.2.1. NMDA subtype of glutamate receptor

The NMDA receptor subtype of the large family of glutamate receptors consists of two separate subunit families, GluN1 and GluN2 (Fig. 2). The heterotetrameric NMDA receptor has a diverse configuration, producing distinct biological and pharmacological effects that change over the lifetime of the organism (Yamakura & Shimoji, 1999). The NMDA receptor requires two co-agonists for its activation, namely L-glutamate and glycine; activation increases cation, predominantly Ca^{2+}, translocation into the cell. The role of the receptor in modulating both physiological synaptic plasticity and pathological excitotoxic neuronal death is predominantly determined by its high permeability to calcium ions when activated. The NMDA receptor has a critical role in the development of the CNS, generation of breathing and locomotor

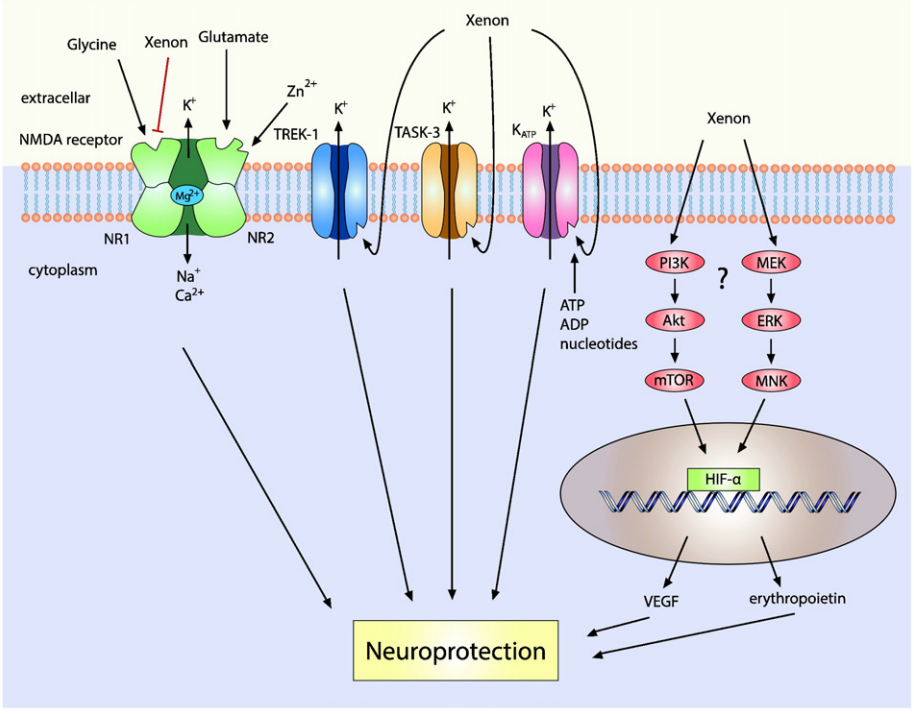

Fig. 2. The mechanism of action of xenon. The NMDA receptor is a heterotetramer receptor which consists of two NR1 and two NR2 subunits. The NR1 subunit has a binding site for glycine and NR2 has one for glutamate and Zn^{2+}. Both glutamate and glycine are needed for NMDA receptor activation. It has been demonstrated that xenon can inhibit the NMDA receptor by competing with glycine at its binding site. Inhibition of the NMDA receptor prevents the influx of Ca^{2+} and Na^+, causing different anesthetic actions. Xenon can also activate TREK-1, TASK-3 and K_{ATP} channels. Activation of these channels allows the efflux of K^+, conferring neuroprotection. It is also noted that K_{ATP} channels can be gated by ATP, ADP and nucleotides. Xenon also upregulates the PI3K-Akt-mTOP and the MARK pathways, although the precise mechanism is not completely understood. The upregulation of these pathways increases the efficiency of the action of HIF-1α, as well as production of its downstream effectors, VEGF and erythropoietin, which are believed to play a role in neuroprotection in ischemic brain injury. ADP, adenosine diphosphate; Akt, AKT serine/threonine kinase 1; ATP, adenosine triphosphate; ERK, extracellular signal regulated kinase; HIF-1α, hypoxia inducible factor-1α; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/extracellular signal regulated kinase; MNK, mitogen-activated protein kinase interacting serine threonine kinase; mTOR, Mammalian target of rapamycin; NMDA, *N*-methyl-D-aspartate; PI3K, phosphatidylinositol-3-kinase; TASK-3, potassium two pore domain channel subfamily K member 9; TREK-1, potassium two pore domain channel subfamily K member 2; VEGF, vascular endothelial growth factor.

rhythms and the processes of learning and memory. Therefore, abnormal expression and altered function of these receptor subtypes have been implicated in various clinical disorders of ongoing neuronal injury, including stroke, Huntington's, Parkinson's and Alzheimer's disease (Kemp & McKernan, 2002; Jansen & Dannhardt, 2003; Chazot, 2004; Farlow, 2004; Wood, 2005).

Xenon inhibits NMDA-evoked currents in hippocampal neurons by 60% at clinically relevant concentrations with little effect on the synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate subtype of the glutamate receptor (Franks et al., 1998), although this selectivity has recently been questioned (Haseneder et al., 2009).

Xenon acts as an NMDA antagonist by competing for the co-agonist glycine binding site (Dickinson et al., 2007) and maintaining the open configuration of the glycine binding site domain (Chazot, 2004).

2.2.2. TREK/TASK two-pore domain potassium channels

The TREK and TASK channels produce background or 'leak' K^+ currents to maintain the excitable membrane in a hyperpolarized state (Fig. 2). These channels are activated, to varying degrees, by anesthetics including xenon, N_2O and cyclopropane, as well as potent volatile anesthetics (Patel et al., 1999; Patel & Honore, 2001a; Patel & Honore, 2001b). The TREK-1 subtype is responsible for neuroprotection by the fatty acid, linolenate (Heurteaux et al., 2004). As xenon produces TREK-1 activation, this is a possible mechanism for its neuroprotective effects (Gruss et al., 2004; Harris et al., 2013; Duprat et al., 2000).

2.2.3. K_{ATP} channels

Xenon activates plasmalemmal ATP-sensitive potassium (K_{ATP}) channels (Bantel et al., 2009). Gated by the intracellular nucleotides ATP and ADP, K_{ATP} channels couple neuronal excitability to its metabolic status (Fig. 2). The channels are inhibited by physiological levels of ATP and, when this nucleotide is depleted by stressors such as hypoxia, the channels are activated and protect against excitotoxicity and ischemic injury (Ballanyi, 2004). At clinically relevant concentrations, xenon has been shown to activate plasmalemmal K_{ATP} channels by almost 50%, and may facilitate xenon-mediated preconditioning against ischemic neuronal injury (Bantel et al., 2009). Xenon is unique amongst the inhalational anesthetics in that it induces neuronal preconditioning in a K_{ATP}-dependent manner.

2.2.4. HIF-1α

Hypoxia-inducible factor 1-alpha (HIF-1α) is subunit of the heterodimeric transcription factor, hypoxia-inducible factor-1, that induces the organism's systemic response to low oxygen concentrations. As cellular oxygen tension drops, HIF-1α is no longer degraded and upregulates downstream effectors, erythropoietin (EPO) and vascular endothelial growth factor (VEGF), by binding to hypoxia-responsive elements in the promoter region of the cognate genes (Fig. 2). The transcriptional activity of HIF-1α on the genes for reparative/restorative proteins, such as EPO and VEGF, make it a major contributor to preconditioning in both the neonatal rat brain and rat retinal neurons (Jones et al., 2006; Grimm et al., 2006).

Xenon produces a sustained increase in HIF-1α activity under normoxic conditions *via* an increase in the translational efficiency of HIF-1α by mTOR regulation through two upstream regulators of mTOR; this is a mechanism for xenon's neuroprotective properties (Ma et al., 2009; Valleggi et al., 2011).

2.2.5. No GABAmimetic action

Whilst most volatile and intravenous anesthetics predominantly act on $GABA_A$ receptors (Haseneder et al., 2009; Salmi et al., 2008), xenon has been found to have no action on C^{11}-flumazenil binding in the living human brain, suggesting that xenon acts independently of the $GABA_A$ receptor system (Salmi et al., 2008). However, in studies involving recombinant $GABA_A$ receptor complexes, xenon has modest GABAergic properties (Hapfelmeier et al., 2000; Yamakura & Harris, 2000).

3. General effects on the developing brain

The developing brain requires the intricate control of different physiological processes, such as the differentiation of neurons from stem cell precursors, the migration of immature neurons to their final locations, axonal and dendritic neuronal outgrowth, synaptic plasticity and synaptic generation between axons and their postsynaptic counterparts. Many of these processes are not limited only to the fetus, but continue during neonatal neural development and throughout early childhood. There are currently only limited data regarding the potential effects of dexmedetomidine and xenon on these intricate processes in the developing brain.

3.1. Anesthetic effects

3.1.1. Dexmedetomidine

As yet, there is no market authorization for the use of dexmedetomidine in children. Despite the apparent safety for the use of dexmedetomidine intraoperatively for appropriately monitored patients (Buck, 2010; Tobias, 2007), there are no long-term outcome studies in pediatric patients.

Regarding possible fetal effects, few studies have investigated the effects of maternally-administered dexmedetomidine on fetal implantation, morphology and behavior (Tariq et al., 2008). Data from preclinical studies suggest that single dose administration of dexmedetomidine to pregnant dams has no adverse effects on the fetus or neonatal pup (Tariq et al., 2008; Chrysostomou et al., 2014; Koroglu et al., 2005; Palanisamy et al., 2009; Neumann et al., 2009). Tariq et al. (2008) conducted a study investigating the effects of subacute and chronic *in utero* exposure of dexmedetomidine on fetal rat development (Tariq et al., 2008). The findings demonstrated that chronic administration of dexmedetomidine anesthesia (0, 5, 10 and 20 μg/kg, subcutaneously; from gestational day 7 to day 19 – the major period of organogenesis) in pregnant Sprague-Dawley rats- was associated with a significant reduction in neonatal pup body weight and crown-rump length. In contrast, a single acute dose (20 μg/kg) of dexmedetomidine, which aimed to mimic systemic analgesia during labor, had no effect on these parameters and, overall, had no adverse effects on postnatal pup morphology, birth weight, crown-rump length, physical growth or postnatal behavioral performance. Neither acute nor chronic exposure resulted in either external malformations or musculoskeletal/anatomical abnormalities.

Various clinical studies also support the notion that dexmedetomidine sedation is associated with few or no adverse effects on the neonate. A phase II/III multicenter trial involving 42 mechanically ventilated neonates was conducted with the aim of investigating the safety, efficacy, and pharmacokinetics of dexmedetomidine in preterm and term neonates (Chrysostomou et al., 2014). The study concluded that dexmedetomidine is safe and effective for sedating both preterm and term neonates, with no significant associated adverse events; however, preterm neonates experienced reduced plasma clearance and a longer elimination half-life. A study recruiting older children, aged 1–7 years, also indicated that dexmedetomidine was effective in providing adequate sedation in children with no associated adverse events or cardiorespiratory instability (Koroglu et al., 2005).

Although significant adverse neurological side effects associated with dexmedetomidine administration in children have not been noted, close cardiovascular monitoring is required due to the potential for hypotension and bradycardia in the mother and fetus, even at clinically-recommended doses (Chassard et al., 1996; Missant et al., 2004). Further commentary on the potential for cardiovascular side effects of dexmedetomidine in this population can be found in Section 7 – Limitations.

3.1.2. Xenon

Lane et al. (1980) reported that pregnant rats exposed to N_2O anesthesia developed skeletal anomalies, numerous macroscopic lesions and

fetal resorption (Lane et al., 1980). Various preclinical studies have confirmed the teratogenic effects of N_2O in rats (Fujinaga et al., 1987). In contrast, preclinical studies investigating the effects of xenon in the developing fetus found that it possessed similar anesthetic properties to N_2O, but without the fetotoxic and teratogenic effects (Lane et al., 1980). Nonetheless, the report is quite sparse on details. Whilst industrial sponsors are obliged to submit data from fetotoxicity and teratogenicity studies to obtain market authorization, the only public documentation of results from comprehensive fetotoxicity and teratogenicity studies are contained in a monograph (Burov, 1999). Pregnant rat dams exposed to 80% xenon for 2 h twice a week from the 1st to the 19th d of gestation resulted in no effect on number of fetuses, sites of implantation, post-implantation mortality, or fetal body weight and length. No skeletal malformations nor developmental defects were noted. Postnatal achievement of physiological milestones, including covering of fur, appearance of incisors, opening of eyes and time until reflexes achieved, was unaffected by xenon administration.

3.2. Analgesic effects

3.2.1. Dexmedetomidine

The analgesic effects of dexmedetomidine, combined with the 'cooperative sedation' that it produces, makes it an effective anesthetic-sparing agent in the perioperative management of neonates and children. However, the long-term effects on neurodevelopment have not been rigorously explored in clinical settings. In a preclinical study reported by Walker et al. (2005), epidural dexmedetomidine was effective in reversing inflammatory hyperalgesia in rat pups aged 3, 10 and 21 days (Walker et al., 2005). Sanders et al. (2005) reported that 7-day-old neonatal rats have a greater sensitivity to the analgesic effects of dexmedetomidine compared to older rats (Sanders et al., 2005). Again, no long-term consequences were explored. When analgesic doses of dexmedetomidine were provided to parturients during cesarean section under general anesthesia, no immediate adverse neonatal events were noted (Palanisamy et al., 2009; Bhana et al., 2000); no long-term effects were explored.

Studies investigating the placental transfer of dexmedetomidine have found that the drug has the ability to cross the placenta, albeit negligibly (Mattingly et al., 2003). The limited transfer of dexmedetomidine from the maternal to fetal circulation is predominantly due to its greater lipophilicity, resulting in enhanced placental retention (Bhana et al., 2000; Ala-Kokko et al., 1997).

4. Molecular effects on neuronal injury

4.1. Apoptosis

Apoptosis, or programmed cell death, has an important role in regulating normal development and tissue remodeling in multicellular organisms; neurotoxic anesthetic agents increase neuro-apoptosis. The molecular processes of apoptosis involve the B cell lymphoma/leukemia-2 (Bcl-2) family of pro-apoptotic and anti-apoptotic regulatory proteins. The delicate balance of these proteins determines mitochondrial membrane integrity and the release of apoptogenic proteins from the mitochondria (Zhao et al., 2003). Bcl-associated death protein (Bad) is a critical pro-apoptotic protein, whose activation is mediated by proto-oncogene proteins c-akt (Akt) through phosphorylation of its serine residues (Koh, 2011). Following its activation, Bad adheres to cytosolic protein 14-3-3 to release Bcl-xL, an anti-apoptotic protein, which inhibits apoptosis by binding to the pro-apoptotic mediator, Bax (Hou et al., 2011; Hsu et al., 1997). Therefore, Bcl-2 and Bcl-xL proteins exert their anti-apoptotic effects by preventing Bax mitochondrial translocation, maintaining mitochondrial membrane potential, and inhibiting cytochrome C release from the mitochondria.

4.1.1. Dexmedetomidine

Dexmedetomidine has been shown to possess neuroprotective properties that protect the brain from injury, including that produced by neurotoxic anesthetics (Lee et al., 2007; Nagahara et al., 2009; Pan et al., 1998; Karege et al., 2002). Whilst there are some data that hint at the reasons for this, the precise molecular mechanisms involved in mediating these effects have not been comprehensively elucidated.

Isoflurane, a neurotoxic anesthetic agent, inhibits Akt and Bad phosphorylation and induces neuroapoptosis in the neonatal rat hippocampus (Li et al., 2014). In addition, isoflurane also induces neurotoxicity by downregulating the ratio of Bcl-2/Bax in both pheochromocytoma 12 (PC12) cells and primary cortical neurons (Wei et al., 2005). Sanders et al. provides evidence demonstrating that dexmedetomidine exerts its neuroprotective effects in an α2-adrenoceptor-dependent manner, resulting in cortical neuroprotection *via* the attenuation of isoflurane-induced neuroapoptosis (Sanders et al., 2009; Sanders et al., 2010). Whilst isoflurane-induced apoptosis is associated with downregulation of pERK and Bcl-2 signaling, it has been found that dexmedetomidine neuroprotection upregulates these critical effectors (Dahmani et al., 2008). Dexmedetomidine also increases other anti-apoptotic proteins, including murine double minute-2 (Mdm-2), and reduces pro-apopotic mediator, p53, which results in protection against ischemic cerebral injury (Engelhard et al., 2003). Thus, modulation of the PI3K/Akt pathway and Bcl-2/Bax ratio in diametrically opposite directions can produce neurotoxicity by isoflurane and neuroprotection by dexmedetomidine. This is consistent with other studies indicating the ability for dexmedetomidine to regulate the pERK neuroprotective signaling cascade and protect against damage *via* α2-adrenergic receptor activation (Xia et al., 2016; Hu et al., 2016; Zhai et al., 2016; Wang et al., 2016).

Independent of α2-adrenoceptor-mediated anti-apoptosis, dexmedetomidine also causes an increase of focal adhesion kinase (FAK) phosphorylation in hippocampal slices exposed to oxygen-glucose deprivation, as well as an increase in the basal concentration of phosphorylated extracellular signal-regulated kinase 1/2 (ERK1/2) (Dahmani et al., 2008; Dahmani et al., 2005). FAK, an important regulator of apoptosis, exerts its anti-apoptotic effects by activating the PI3K/Akt survival pathway, with the simultaneous activation of nuclear factor-κB and the induction of inhibitor-of-apoptosis proteins (IAPs: cIAP-1, cIAP-2, XIAP). This ultimately results in the attenuation of apoptosis by preventing activation of the caspase-3 cascade. Therefore, the inhibition of FAK may act as an additional mechanism by which dexmedetomidine induces its neuroprotective effects.

In addition to its anti-apoptotic effects, dexmedetomidine has also demonstrated the ability to exert neuroprotection by inhibiting calcium influx, scavenging glutamate and reducing NMDA receptor activation (Ma et al., 2005a).

4.1.2. Xenon

Similar to the action of dexmedetomidine, it has been postulated that xenon acts by upregulating pro-survival genes, whilst the application of alternative anesthetic agents, such as N_2O, do not have this effect (Ma et al., 2006; Wilson et al., 1996; Ma et al., 2005b). This may at least partly explain why the combination of N_2O with isoflurane increases apoptosis, whereas xenon significantly reduces isoflurane-induced apoptosis, often to a value similar or identical to the control cohort (Ma et al., 2007).

It is thought that the protective effect of xenon pre-treatment against isoflurane and N_2O-induced neuronal apoptosis may be due to the inhibition of mitochondria-induced activation of the caspase-3 pathway (Shu et al., 2010; Ma et al., 2007). Xenon exposure also upregulates the expression of anti-apoptotic Bcl-2, whilst downregulating the pro-apoptotic tumor suppressor, transcription factor p53 (Shu et al., 2010). Xenon has been shown to have no significant effect on cytochrome C levels. In addition to these processes, xenon pre-treatment also increases CREB phosphorylation and BDNF expression(109–111).

Interestingly, in developing mice xenon does prevent isoflurane-induced neurotoxicity, although xenon alone does produce mild neurotoxicity (Wei et al., 2007). Whilst shorter periods of xenon exposure (<2 h) is associated with neuroprotection, longer periods may contribute to mild toxicity in the developing brain (Shu et al., 2010; Cattano et al., 2008). In addition, a recent *in vitro* study conducted by Brosnan et al. found that xenon caused apoptosis and neurotoxicity in hippocampal slice cultures from 7-day-old-rats at minimum alveolar concentration (MAC) and above (Brosnan & Bickler, 2013); the apoptosis was less than that seen with the equi-anesthetic concentrations of the volatile anesthetics.

4.2. Brain derived neurotrophic factor (BDNF)

BDNF is part of the neurotrophin family of growth-promoting proteins that are responsible for various neuronal processes, including neuronal survival, axonal sprouting, and synaptic plasticity *via* neurotrophic tyrosine kinase receptor type 2 (TrkB). BDNF is predominantly stored in platelets, but may also be synthesized and secreted by vascular endothelium, visceral epithelium and inflammatory cells, such as activated T-helper cells (Radka et al., 1996; Lommatzsch et al., 1999; Nakahashi et al., 2000; Hohlfeld et al., 2007). Several murine studies have indicated a correlation between BDNF and neuronal functionality, as demonstrated by learning, memory and other advanced neuronal functions (Chao et al., 2006). The relationship between BDNF concentration and the presence of clinical neuropsychiatric diseases is highlighted by reports that clinically depressed patients have lower levels of BDNF compared to controls (Martinowich et al., 2007; Lee et al., 2007). The elevation of BDNF within the CNS is associated with the attenuation of ischemia- and neurodegenerative-mediated neuronal injury (Nagahara et al., 2009). Serum BDNF concentrations have been found to be a good indicator of cortical BDNF levels, indicating that the determination of serum BDNF levels may reflect BDNF concentrations in the brain (Pan et al., 1998; Karege et al., 2002).

4.2.1. Dexmedetomidine

In a model of neonatal glutamate-induced neuronal injury, dexmedetomidine was found to be neuroprotective, in association with an increase in BDNF expression; the neuroprotection is attenuated by neutralizing antibodies to BDNF (Degos et al., 2013). Astrocytes are the source of BDNF following dexmedetomidine administration and it is noteworthy that both dexmedetomidine-induced BDNF expression and dexmedetomidine-induced astrocyte expression of BDNF are dependent on the ERK1/2 pathway (Reyland et al., 2000).

It is important to note that, whilst activation of the TrKb-BDNF pathway is critical in mediating the effects of BDNF; the BDNF precursor, pro-BDNF, can also be released into the extracellular space (Kolarow et al., 2007). In fact, pro-BDNF (35 KDa) has been shown to promote cell death, indicating that the balance between BDNF and pro-BDNF may be crucial (Woo et al., 2005).

Various anesthetic agents cause a reduction in BDNF plasma concentrations and inhibit the release of BDNF from cortical neurons, whilst dexmedetomidine acts to reverse this (Degos et al., 2013; Lu et al., 2006; Head et al., 2009). The anesthetic-mediated reduction in plasma BDNF and increase in pro-BDNF may partly explain how anesthetics induce neurotoxicity, as well as indicate a potential mechanism by which dexmedetomidine confers neuroprotection.

4.3. Anti-excitotoxicity

The term 'excitotoxicity' was first coined by John Olney (1969) to describe a process whereby overstimulation of glutamate receptors, particularly the NMDA subtype, results in excessive calcium influx into cells, triggering a cascade that ultimately leads to neuronal death (Olney, 1969). Both *in vitro* and *in vivo* evidence demonstrate that NMDA receptor antagonists can protect against neuronal injury and post-surgical cognitive decline (Sarraf-Yazdi et al., 1998; Harada et al., 1999; Popovic et al., 2000; Kudo et al., 2001; Arrowsmith et al., 1998). The main deterrent to the use of NMDA antagonists as neuroprotective agents is the potential for profound psychotomimetic behavioral changes (Malhotra et al., 1996). Studies investigating the neurotoxic effects of NMDA receptor antagonists, ketamine, phencyclidine (PCP), dizocilpine maleate (MK801) and N_2O, have demonstrated that these agents are associated with histological changes in the region of the posterior cingulate and retrosplenial (PC/RS) cortices (Olney et al., 1989; Allen & Iversen, 1990); these pathological changes may be responsible for the associated behavioral changes.

4.3.1. Xenon

Ma et al. (2002) produced an *in vitro* rat model of brain injury to investigate whether xenon is capable of exerting neuroprotection without histological changes in the PC/RC cortices using the expression of c-Fos, a rapid and sensitive marker of neuronal stress and injury; xenon exhibits neuroprotective properties without concomitant neurotoxicity. While the reason for xenon's divergence remains to be fully understood, it is noteworthy that ketamine and N_2O activate dopamine receptors or increase dopamine release *in vivo* and *in vitro*, whereas xenon has no effect on dopaminergic pathways (Murakawa et al., 1994; Moghaddam et al., 1997; Lindefors et al., 1997). As antipsychotic medications usually have dopamine D2 receptor antagonistic properties, it is likely that the increase in dopamine may produce the psychotomimetic properties of anesthetics, such as ketamine and N_2O.

Xenon's efficacy as an *anti*-excitotoxic agent is probably due to a combination of its potent NMDA antagonism, ability to freely cross the blood-brain barrier (BBB) and low blood/gas solubility (Goto et al., 1998). These properties provide xenon with the capability for rapid inflow and washout, as well as a reduction in the risk of adverse reactions (Bedi et al., 2003; Latchaw et al., 1987).

5. Whole animal models of neuroprotection

5.1. Perinatal asphyxia

Neonatal neurologic hypoxic-ischemic injury, also referred to as perinatal asphyxia or hypoxic-ischemic encephalopathy, is a severe neurological condition that affects newborns. Although its incidence has decreased in recent years due to improvements in perinatal monitoring and early obstetrical and neonatal interventions, unexpected hypoxic-ischemic injury still occurs, even in the developed world (Lynch & Nelson, 2001; Wu et al., 2004; Smith et al., 2000). Perinatal asphyxia occurs in up to 3/1000 live births in the UK, with over 1000 cases of moderate to severe hypoxic-ischemic injury expected each year, and is associated with a risk of death and severe handicap in 25% and 75% of patients, respectively (Kurinczuk et al., 2010; Vannucci & Perlman, 1997; Low et al., 1988; Finer et al., 1981). Etiological factors involved in hypoxic-ischemic injury include both obstetrical complications, such as umbilical cord compression, as well as maternal factors, such as abnormal variations in blood pressure. The production of oxygen free-radicals and the release of excitatory neurotransmitters, including catecholamines and glutamate, results in an elevation in intracellular calcium and culminates in excitotoxic neuronal death. As the neonatal brain is immature, it is more susceptible to even short periods of oxygen deprivation (Ferriero, 2004). Both pre- and perinatal hypoxic-ischemic injury have been shown to contribute significantly towards childhood morbidity and mortality, clinically manifesting as seizures, mental retardation and motor dysfunction (Perlman, 2004).

5.1.1. Dexmedetomidine

Due to preclinical evidence indicating dexmedetomidine's ability to provide neuroprotection before or during brain ischemia (Ma et al., 2004a; Kuhmonen et al., 1997; Cosar et al., 2009; Hoffman et al., 1991; Maier et al., 1993; Zhu et al., 2013), it has been suggested that it may

possess a role in attenuating perinatal asphyxia. In addition, the fact that dexmedetomidine is able to cross the BBB and stimulate α2-adrenoceptors centrally provides further evidence for its potential to reduce hypoxic-ischemic damage in the brain.

Dexmedetomidine has demonstrated significant neuroprotective effects in animal neonatal models, particularly in the hypoxic-ischemic neonatal brain (Engelhard et al., 2003; Paris et al., 2006; Jolkkonen et al., 1999). A dose-dependent reduction in white matter loss and a significant reduction in neurologic functional deficit has been demonstrated in neonatal rats exposed to dexmedetomidine prior to asphyxia. However, the potential for any long-term deleterious neurological effects following dexmedetomidine exposure in neonates was not addressed.

Ma et al. (2004a, 2004b) produced an *in vivo* murine model of neonatal asphyxia and reported the ability for dexmedetomidine to produce dose-dependent protection against brain matter loss, as well as reduce neurologic functional deficit (Ma et al., 2004a). Meanwhile, administration of the α2A-adrenoceptor subtype-preferring antagonist, BRL44408, resulted in a reversal of dexmedetomidine-mediated neuroprotection. Overall, these *in vivo* results suggest that dexmedetomidine elicits its neuroprotective effects by activating the $\alpha 2_A$ adrenergic receptor subtype, resulting in an attenuation of neonatal neurologic hypoxic-ischemic injury.

Dexmedetomidine post-conditioning has demonstrated the ability to improve neurological outcomes after brain hypoxic-ischemic injury in neonatal rats. Ren et al. (2016) demonstrated neuroprotective effects that are evident both 7-days and 28-days post-dexmedetomidine intraperitoneal administration, following left brain hypoxic-ischemic injury in Sprague-Dawley rats (Ren et al., 2016). At the 28-day assessment, rats were old enough to undertake neurological and cognitive functional testing, with rotarod used to test motor, sensory and co-ordination function and Barnes maze and fear conditioning to assess learning and memory. Dexmedetomidine administration resulted in a significant improvement in rotarod, Barnes maze and fear conditioning testing, suggesting the ability for dexmedetomidine post-conditioning to improve long-term neurological outcomes following brain hypoxic-ischemic injury in neonatal rats. It is important to note that these beneficial effects are only present if dexmedetomidine is administered within 1 h of neuronal injury. Regarding dexmedetomidine's post-conditioning potential, hippocampal neuronal injury following transient global ischemia in adult gerbils was not affected by dexmedetomidine post-conditioning, however, post-conditioning significantly reduced traumatic brain injury in an *in vitro* hippocampal slice model (Kuhmonen et al., 1997; Schoeler et al., 2012).

It is important to note that perinatal asphyxia has the ability to affect the pharmacokinetics (PK) of dexmedetomidine. A PK model of piglet perinatal asphyxia indicated that dexmedetomidine clearance is reduced by almost 10-fold in the newborn piglet following hypoxic-ischemic brain injury, followed by therapeutic hypothermia, compared to exposure to adults (Ezzati et al., 2014). Clearance is further reduced in severe asphyxia with multi-organ failure. These pharmacokinetic alterations were shown to significantly increase the incidence of adverse cardiovascular events, emphasizing the importance of further PK studies to elucidate the potential toxicity associated with dexmedetomidine administration in the newborn.

High supplemental oxygen therapy in the management of perinatal asphyxia can result in hyperoxia that disturbs intracellular redox homeostasis and can result in further neurological injury, especially to preterm infants (Deulofeut et al., 2007; Wright & Dennery, 2009; Saugstad et al., 2012). Oxidative stress is induced *via* abnormal regulation of the glutathione ratio, increased lipid peroxidation and upregulation of pro-inflammatory cytokine release (Felderhoff-Mueser et al., 2004; Sifringer et al., 2010; Sifringer et al., 2013; Sifringer et al., 2009). These processes ultimately result in significant neurodegeneration and inhibition of neuronal maturation in the developing brain (Endesfelder et al., 2014; Brehmer et al., 2012). Sifringer et al. (2015) reports that dexmedetomidine (1, 5, or 10 μg/kg) attenuates oxygen-induced brain injury in 6-day-old neonatal Wistar rats by reducing lipid peroxidation (assessed by malondialdehyde), by downregulating IL-1β, and by restoring the glutathione ratio (Sifringer et al., 2015). Hyperoxia-exposed rats have been shown to experience a 5-fold increase in cortical and deep gray matter cellular degeneration, whilst the study by Sifringer et al. demonstrates that dexmedetomidine treatment significantly decreases degeneration in these brain regions (Endesfelder et al., 2014; Kaindl et al., 2008; Sifringer et al., 2015). These findings are consistent with other whole animal studies that have confirmed the neuroprotective effects of dexmedetomidine (Ma et al., 2004a; Kuhmonen et al., 1997; Cosar et al., 2009; Eser et al., 2008; Duan et al., 2014; Xiong et al., 2014). It is noteworthy that dexmedetomidine may induce neuroapoptosis within primary sensory brain regions when administered at higher frequencies (Pancaro et al., 2016). These results suggest that dexmedetomidine may exhibit potential toxicity, thus warranting further whole animal studies to investigate this proposition.

5.1.2. Xenon

Although many NMDA-receptor subtype antagonists have demonstrated the remarkable ability to attenuate neuronal injury, these results have not been translated into clinical practice due to the relative inability for many of these to efficiently cross the BBB. As xenon is a small apolar atom that rapidly equilibrates with the brain when administered in inspired gas, xenon has a significant advantage over other NMDA antagonists and has the potential to be a promising and clinically viable neuroprotectant.

Similar to dexmedetomidine, the largest *in vivo* evidence base for xenon's neonatal neuroprotective effects are in models of hypoxic-ischemic injury. As the neurotoxic processes underlying perinatal asphyxia continue evolving after delivery, the development of therapeutic agents to attenuate further neuronal injury are warranted.

Seven-day-old rats receiving 90-min hypoxic insult, following unilateral carotid ligation, demonstrated that three hours of xenon administration, following hypoxia-ischemia, affords significant short-term neuroprotection (Dingley et al., 2006). Furthermore, exposure to xenon was associated with 80% less global neuronal injury, 60% reduction in cortex/white matter injury and a reversal of hippocampal and thalamic damage to baseline levels. These improvements were noted with the administration of a sub-anesthetic (50%) dose of xenon in spontaneously breathing neonatal rats; this dose is clinically feasible in sick infants as it allows for the delivery of up to 50% oxygen in the inhaled gas mixture. In addition, arcuate nucleus injury provoked by NMDA is significantly reduced in a dose-dependent manner by xenon, whilst a rat cardiopulmonary bypass model demonstrated that xenon administration during the procedure is associated with a reduction in post-surgical neurocognitive dysfunction (Wilhelm et al., 2002; Ma et al., 2003). The NMDA antagonist, MK801, attenuates neuronal injury to a lesser extent, thus further indicating that xenon produces its neuroprotective effects *via* more than one mechanism (Ma et al., 2003).

As well as dexmedetomidine, xenon has been shown to be an effective post-conditioning agent by conferring neuroprotection following hypoxic-ischemic injury. In an *in vivo* model of neonatal asphyxia, Ma et al. (2006) found that xenon reduced hypoxic-ischemic injury in 7-day-old rats and was associated with a reduction in infarction size at 7-day post-injury assessment (Ma et al., 2006). In addition, long-term sustained improvement was noted at 30-days following injury. Xenon's likely mechanism of producing neonatal neuroprotection against hypoxic-ischemic injury is *via* upregulation of pCREB-regulated synthesis of pro-survival proteins against neuronal injury. It is interesting to note that, despite its NMDA antagonistic effects, N_2O does not precondition and is not associated with an increase in pCREB.

During the first 2 weeks of life, a complete NMDA receptor blockade may have pro-apoptotic effects in the developing brain (Ikonomidou et al., 1999; Hansen et al., 2004). In light of this, it is important to note that xenon causes only partial antagonism of the NMDA receptor

(reducing currents by ≈60%), even at concentrations as high as 80%, a concentration that is unlikely to be clinically attained (Franks et al., 1998).

Xenon's potent preconditioning ability, combined with its effective neuroprotective capabilities and absence of fetotoxicity, makes it a promising agent in the management of neonatal asphyxia.

5.1.2.1. Xenon and hypothermia. Hypothermia is currently the only clinically proven intervention that improves patient outcomes following perinatal asphyxia, most probably by reducing glutamate release and subsequently attenuating excitotoxic injury. The combination of xenon and hypothermia provides greater protection after neonatal hypoxic-ischemic injury than either treatment alone (Hobbs et al., 2008; Martin et al., 2007; Ma et al., 2005c). As hypothermia causes a pre-synaptic reduction in glutamate release and inhibits activation of the apoptotic cascade proximally, the asynchronous administration of both agents results in a significant reduction in neurotoxicity and attenuates the pathogenesis of neonatal hypoxic-ischemic injury (Martin et al., 2007). Remarkably, Hobbs et al. demonstrated that the combination of both treatments results in almost complete functional improvement with both short- and long-term effects, accompanied by significant improvements in histopathology (71%) (Hobbs et al., 2008). These findings suggest that the two interventions may have a synergistic effect in conferring neuroprotection. However, a recent study conducted by Sabir et al., investigating the neuroprotective effects of xenon with hypothermia on 120 7-day-old rat pups following unilateral carotid artery ligation, found that immediate therapeutic hypothermia, with or without additional 50% inhaled xenon, does not provide neuroprotection one week after severe hypoxic-ischemic brain injury (Sabir et al., 2016). The presence of these confounding findings warrants further investigation, whilst clinical trials investigating the neuroprotective effects of therapeutic hypothermia and xenon may shed further light on these inconsistencies, as discussed in Section 6 – Clinical Trials of Neurological Injury.

5.2. Anesthetic-induced developmental neurotoxicity

Various commonly used anesthetic agents have neurotoxic and neurodegenerative effects *in vivo* after exposure in the neonatal period (Jevtovic-Todorovic et al., 2003; Liang et al., 2010; Istaphanous et al., 2011; Pearn et al., 2012; Jevtovic-Todorovic et al., 1998; Yan & Jiang, 2014; Sanders et al., 2008; Slikker et al., 2007). For example, 2.5% sevoflurane anesthesia has been found to cause an immediate increase in neuroapoptosis within the fetal mouse brain, resulting in progressive learning and memory impairment which may also affect further development (Zheng et al., 2013). Similarly, the administration of 1.7% isoflurane daily for 35 min for five consecutive days, from postnatal day-14, is associated with significant cognitive impairment compared to control cohorts (Zhu et al., 2010). Isoflurane-mediated cognitive impairment correlates with a persistent reduction in the hippocampal neural stem cell pool and dysfunctional neurogenesis. In addition, intraperitoneal propofol administration causes significant cortical and hippocampal cell death, whilst repeated neonatal exposure to propofol is associated with more significant long-term deleterious neurological sequelae than a single exposure during the neonatal period (Yu et al., 2013; Milanovic et al., 2010). Propofol-induced cognitive dysfunction and memory impairment is associated with a significant reduction in glutamate neurotransmission in cortical and hippocampal regions of adult rats. Even with sub-anesthetic dosing, hippocampal dysfunction is a common finding in isoflurane-treated animals, manifesting as an abnormal response to contextual fear conditioning (Jevtovic-Todorovic et al., 2003; Fredriksson et al., 2007). In terms of functional changes, isoflurane has been found to have less effect on the acquisition of short-term memory, but more significant deleterious effects on long-term memory.

Clinical studies addressing anesthetic-induced developmental neurotoxicity have been mostly observational, in which children exposed to surgery and anesthesia are compared to non-exposed children (Loepke & Soriano, 2008; DiMaggio et al., 2009; Hansen et al., 2011; Ing et al., 2012; Wilder et al., 2009; Ing et al., 2014). From these, it is impossible to establish whether any observed toxicity is due to the anesthetic itself, or factors that include the surgery and the underlying condition that necessitated the surgery. The observational studies may be retrospective, in which the "control" cohort is population-based, or ambidirectional in which previously anesthetized children are identified and prospectively assessed longitudinally. Recently, a sibling-controlled clinical trial reported that administration of a single, short general anesthetic did not affect neurocognitive performance during adolescent years (Sun et al., 2016); a similar conclusion was reached in the interim analysis of the first prospective randomized clinical trial (Davidson et al., 2016).

Whilst conclusive causal evidence for anesthetic-induced developmental neurotoxicity is still lacking, it is notable that the FDA have issued a warning regarding the *potential* for toxicity in pediatric patients under three years of age who receive prolonged and/or multiple general anesthetics or sedatives (U.S. Food and Drug Administration, 2016). Therefore, the search to find anesthetic agents that can attenuate these neurotoxic effects is timely and highly warranted, with various preclinical studies indicating that both dexmedetomidine and xenon may have the ability to do so.

5.2.1. Dexmedetomidine

In vivo studies have found that dexmedetomidine dose-dependently reduces isoflurane-induced injury in the hippocampus and thalamus (Sanders et al., 2009; Sanders et al., 2010). Remarkably, the neurological dysfunction induced by isoflurane is attenuated with co-administration of dexmedetomidine (Sanders et al., 2009).

According to Sanders et al. (2010), dexmedetomidine protects against isoflurane-induced neurotoxicity by inhibiting isoflurane-induced caspase-3 expression and attenuating cortical apoptosis (Sanders et al., 2010). Postnatal day-7 rat pups were exposed to 6 h of isoflurane (0.75%), with subsequent administration of dexmedetomidine in escalating doses. Whilst isoflurane exposure resulted in neuroapoptosis throughout the cortex compared to air (327 ± 80 *vs.* 34 ± 9; $P < 0.05$), dexmedetomidine (25 μg/kg) did not induce apoptosis (51 ± 19; $P > 0.05$ *vs.* air) but reduced the number of isoflurane-induced caspase-3-positive neurons to 188 ± 29 ($P < 0.05$). The negative regulation of caspase-3 expression by α2-adrenoceptor agonists in the neonatal cerebral cortex has also been confirmed in previous studies (Men'shanov et al., 2007). Here, further protection was not conferred in a dose-dependent manner, with dosage escalation to 50 μg/kg (189 ± 59) and 75 μg/kg (166 ± 23) having no further neuroprotective effect ($P > 0.05$ relative to dexmedetomidine 25 μg/kg). It is important to note that, although three doses of 25 μg/kg over a 6 h period to 7-day neonatal rat pups did not induce neuroapoptosis, when the frequency was increased to six doses in a 10 h period, neuroapoptosis may be seen in primary sensory brain regions (Pancaro et al., 2016). These results suggest that combination therapies, perhaps with concurrent hypothermia, may act synergistically with dexmedetomidine to confer maximal cortical neuroprotection against isoflurane-mediated neurotoxicity. In addition to upregulating caspase-3 expression, isoflurane exposure also reduces the expression of anti-apoptotic signaling pathways mediated by Bcl-2 and pERK1 and 2, in a similar mechanism to neonatal brain injury. Furthermore, dexmedetomidine can ameliorate the negative effects on pERK signaling. Despite prominent neuroprotection of the thalamus and hippocampus, it is important to note that isoflurane-mediated cortical neurotoxicity is not entirely attenuated with dexmedetomidine administration (Sanders et al., 2009).

Unfortunately, there are currently a lack of comparative *in vivo* data of dexmedetomidine *vs* a panel of neurotoxic anesthetic agents; this

warrants further research in order to ascertain the precise neuroprotective capabilities of dexmedetomidine against sevoflurane-, ketamine- and N_2O-induced neurotoxicity. Despite an abundance of *in vitro* data implicating dexmedetomidine in the attenuation of anesthetic-mediated neuronal injury, there is currently limited convincing information to propagate its use in humans either with or after anesthesia exposure.

5.2.2. Xenon

As mentioned previously, it is interesting that xenon has been shown to be neuroprotective when administered before, during or after neuronal injury, whilst other NMDA antagonists seem to have the opposite effect. This neuroprotective effect has also been translated into *in vivo* studies investigating the ability of xenon to attenuate anesthetic-induced neurodegeneration in the developing brain.

In vivo, xenon was found to significantly decrease the number of caspase-3 positive cells induced by the combination of 70% N_2O and 0.75% isoflurane treatment (6 h at 1 atmospheric ambient pressure) in 7-day-old Sprague-Dawley rat pups (Shu et al., 2010). In addition, rats pretreated with N_2O display less freezing compared to xenon-pretreated animals, indicating that xenon dampens hippocampal neuroapoptosis. The increase in caspase-3-mediated apoptosis with N_2O + isoflurane is due to direct effects on neural tissue, whilst xenon is thought to inhibit mitochondria-induced activation of the caspase-3 pathway, favorably modulating the ratio of pro- and anti-apoptotic proteins and ultimately attenuating the resulting cognitive dysfunction.

Furthermore, unlike N_2O which enhances isoflurane-induced neuronal injury, xenon protects against isoflurane-induced neuronal apoptosis in a concentration-dependent manner, as reflected by caspase-3 immunostaining (Ma et al., 2007). Remarkably, xenon has been shown to reduce isoflurane-induced neuronal apoptosis to a level that is indistinguishable to the apoptosis observed with air exposure. Overall, a comparison of clinically relevant anesthetic regimens, namely isoflurane and N_2O *vs.* isoflurane and xenon, demonstrates a statistically significant decrease in the level of neuronal apoptosis with the latter treatment ($P < 0.01$).

In keeping with the potent volatile anesthetic agents, xenon also preconditions against subsequent injury through processes that involve K_{ATP} channels. However, unlike the potent volatile anesthetics that mediate preconditioning through channels in the mitochondrial compartment, xenon acts *via* channels confined to the plasmalemma (Bantel et al., 2009). Furthermore, while volatile anesthetics act on the sulfonylurea receptor-1 subunit of K_{ATP} channels, xenon has no activity on this subunit (Bantel et al., 2010).

It is important to note some paradoxical *in vivo* results regarding xenon's neuroprotective effects. In the infant mouse brain, xenon may be responsible for triggering neuroapoptosis; yet in combination with isoflurane, xenon retains its anti-apoptogenic activity whilst also increasing anesthetic depth (Cattano et al., 2008). Although this evidence does not directly conflict with data that suggest xenon attenuates isoflurane-mediated neuronal apoptosis, it raises the question of the extent of xenon's non-neurotoxic safety profile (Ma et al., 2007).

Further *in vivo* studies are certainly required in order to investigate xenon's precise ability to provide neuroprotection against anesthetic-induced neuronal injury, whilst also ascertaining the true extent of its apoptogenic effects.

5.3. Combination of dexmedetomidine and xenon

As both dexmedetomidine and xenon have demonstrated neuroprotective properties independently and *via* distinct receptors, studies have been conducted to investigate the interaction between the two agents and appraise their effects on neuronal injury in the developing brain.

Whilst there is some *in vitro* evidence evaluating the effects of combination treatment, *in vivo* data are currently limited. Ma et al. (2004a, 2004b) were one of the first groups to address this hypothesis *in vitro*, using a primary co-culture of neuronal and glial cells from the cerebral cortex of neonatal mice, and determined that dexmedetomidine and xenon interact in an additive fashion (Ma et al., 2004b).

At doses that are individually not neuroprotective, the combination of dexmedetomidine and xenon has demonstrated the ability to produce significant neuroprotective effects following right common carotid artery ligation and 90 min of hypoxia in postnatal rats aged 7-days (Rajakumaraswamy et al., 2006). In combination, each agent caused a reduction in the dosage needed of the other to elicit the same extent of neuroprotection when administered on its own, whilst isobolographic analysis suggests that the combined effect of the two agents is additive. As well as causing a reduction in the area of infarction, data from neurological functional studies indicate that the combined effect of dexmedetomidine and xenon causes a long-lasting inhibition of late neurological dysfunction. It is possible that the synergistic effect of the two agents is due to an interaction that reduces intracellular Ca^{2+} concentration, thus protecting against excitotoxic neuronal injury. This is supported by the fact that both dexmedetomidine and xenon cause a reduction in NMDA receptor-mediated Ca^{2+} influx in cells exposed to hypoxia. In addition, both agents also increase anti-apoptotic protein Bcl-2 during hypoxic ischemic injury, which may also contribute to the additive effects of the two agents.

Overall, only one *in vivo* study exists investigating the neuroprotective effects of combination treatment. Whilst current evidence does indicate the efficacy of combined therapy in attenuating hypoxic-ischemia-induced brain injury in paradigms of neonatal asphyxia, further *in vivo* studies are required to fully elucidate a possible synergistic relationship between the two agents.

6. Clinical models of neurological injury

6.1. Dexmedetomidine

There is currently limited clinical evidence for the neuroprotective effects of dexmedetomidine in children following neurological injury. In addition, there is no literature describing the long-term effects of dexmedetomidine on memory acquisition, recall, and amnesia in children; this is probably due to the inherent challenges associated with designing and conducting such a trial in children. As a result, clinical evidence for the neuroprotective effects of dexmedetomidine in children is limited to cases of delirium following anesthetic administration, and sedation in critical care settings.

6.1.1. Emergence delirium

Children recovering from general anesthesia frequently experience a clinical phenomenon described as emergence delirium (ED) or agitation, for which no prophylactic or therapeutic interventions have been identified. ED is most commonly observed following sevoflurane exposure, with an associated incidence as high as 67%, likely due to the psychological and neurological immaturity of children, rapid emergence, the concentration of residual sevoflurane and sevoflurane-mediated catecholamine release (Cravero et al., 2000; Beskow & Westrin, 1999; Lapin et al., 1999; Voepel-Lewis et al., 2003; Lerman et al., 1996; Shibata et al., 2005; Yasui et al., 2007). ED is associated with poorer patient recovery and higher complication rates. A double-blind randomized prospective study conducted by Shukry et al. (2005) demonstrated that continuous perioperative infusion of dexmedetomidine 0.2 $\mu g\ kg^{-1}\ h^{-1}$ reduces the incidence post-sevoflurane ED in children, whilst also decreasing the frequency of ED episodes (Shukry et al., 2005).

6.1.2. Sedation in pediatric critical care settings

Within the pediatric population, dexmedetomidine has been shown to preserve epileptiform activity in children suffering from seizure disorders (Mason et al., 2009; Souter et al., 2007). This facilitates the localization and identification of seizure foci, reducing the delay in EEG

interpretation. Therefore, dexmedetomidine may be a uniquely valuable sedative agent in children in whom EEG monitoring is required.

A case report by Tobias investigated the effects of dexmedetomidine sedation, in combination with hypothermia, in 2 pediatric patients with traumatic brain injury (Tobias, 2008). The report found that adequate sedation was achieved and that patients had good long-term neurologic outcomes. However, when hypothermia was used in a sedative regimen including both dexmedetomidine and remifentanil, the patients developed clinically significant bradycardia. These findings indicate that dexmedetomidine may be a viable sedative agent in pediatric patients with traumatic brain injury in critical care, however, large-scale trials are required to confirm this assertion, as well as to fully elucidate dexmedetomidine's cardiovascular side-effect profile in children with neurologic injury.

6.2. Xenon

6.2.1. Hypoxic ischemic injury

As discussed previously, hypoxic ischemic injury is an important clinical phenomenon in the neonate that is associated with neurological disorders such as cerebral palsy and developmental delay.

Dingley et al. (2014) conducted a xenon feasibility study in cooled infants with neonatal encephalopathy (Dingley et al., 2014). The single-arm, dose-escalation feasibility study recruited 14 cooled infants with neonatal encephalopathy and found that xenon was not associated with any significant respiratory or cardiovascular effects. In addition, xenon conferred increased sedation and suppressed seizures and background electroencephalographic activity. The authors concluded that breathing 50% xenon for up to 18 h, accompanied with 72 h of hypothermia, was feasible and associated with no adverse effects at 18 months' follow-up. Importantly, xenon demonstrated rapid reversal of both clinical and EEG depression, clinically characterized by infants opening their eyes and reinitiating gross motor movements within 1–2 min.

These findings are supported by results produced in a pilot study by Thoresen et al. (2011) (Thoresen et al., 2011). The 'CoolXenon' clinical feasibility study involved xenon administration to 12 infants with neonatal encephalopathy undergoing therapeutic hypothermia. The authors concluded that the addition of up to 50% xenon for up to 12 h had no deleterious effects on blood pressure, heart rate or FiO_2. Xenon was found to have a potent sedative effect, associated with fast onset and offset characterized by the recovery of spontaneous movements within 2 min of xenon discontinuation.

The Total Body hypothermia plus Xenon (TOBY-Xe) study is the largest proof-of-concept, open-label, randomized controlled trial investigating the effects of moderate hypothermia plus inhaled xenon (within 6 h of birth) *vs.* moderate hypothermia alone after birth asphyxia (Azzopardi et al., 2015). The study enrolled 92 infants, 36–43 weeks of gestational age, 46 of whom were randomly assigned to cooling only, and 46 to a combination of xenon and cooling; xenon administration began at a median of ~9 h after birth. The authors' primary outcomes were reduction in lactate to *N*-acetyl aspartate ratio in the thalamus and in preserved fractional anisotropy within the posterior limb of the internal capsule, with outcomes assessed by magnetic resonance spectroscopy and magnetic resonance imaging (MRI), respectively, within 15 days of birth. Although xenon administration in the clinical setting was deemed feasible and was not associated with any serious adverse events, there was no significant enhancement of the neuroprotective effect of cooling with the addition of xenon after birth asphyxia.

Further evidence exists to support the viability of xenon's use in the clinical setting. The study by Dingley et al. (2014) addressed the two main factors that currently limit the use of xenon in clinical practice; namely expense and atmospheric scarcity. The study utilized a closed-circuit xenon delivery system, which required a net gaseous use of only 0.29 L/h in order to maintain a stable 50% concentration. The overall xenon requirement was estimated at 0.52 ± 0.18 L/h, whilst xenon is currently priced at approximately $30/L. Attempts should therefore continue to reduce the cost of xenon in order to improve its clinical viability (Chakkarapani et al., 2009).

One phase I trial is currently ongoing in the United Kingdom in order to investigate the efficacy and safety profile of the xenon-hypothermia combination in the pediatric population of patients with hypoxic-ischemic injury (Thoresen, 2014).

Overall, although there is significant evidence to indicate that xenon may be a clinically viable adjunct to conventional hypothermia, its efficacy in enhancing clinical neuroprotection is still unconfirmed in any large-scale pediatric trial. In addition, the precise concentration and duration of xenon therapy in newborns to confer neuroprotection remains to be elucidated.

7. Limitations

Whilst there is potentially much to be gained by using dexmedetomidine and/or xenon to restrict the need for potentially neurotoxic anesthetic agents, there are issues inherent in the pharmacology of these agents that must be considered as possible limitations.

7.1. Dexmedetomidine

The adverse effects of dexmedetomidine are an extension of its pharmacologic properties and mostly affect the cardiovascular system. Dexmedetomidine possesses a, seemingly paradoxical, biphasic effect on blood pressure, with hypotension at clinically-recommended doses and hypertension at higher concentrations or following bolus administration (Potts et al., 2010). The elevated blood pressure occurs due to a direct vasoconstrictive effect mediated by α-2B adrenoceptor activation on the smooth muscle cells lining resistance vessels (Link et al., 1996). The reduction in blood pressure is due to a limitation of the postganglionic release of potent vasoconstrictors from the sympathetic nervous system (Kurnik et al., 2008; Mason et al., 2014). Bradycardia is an expected occurrence following administration of dexmedetomidine due to both a sympatholytic effect on the cardio-accelerator nerve, as well as a vagomimetic effect (Petroz et al., 2006). Treatment of bradycardia, when necessary, is quite responsive to both vagomimetics and positive chronotropic agents (Mason & Lonnqvist, 2015). Due to the tendency for extreme bradycardia, dexmedetomidine is best avoided in patients that are on drugs that predispose to bradycardia and hypotension, including digoxin, β-adrenergic blockers and calcium channel blockers (Mahmoud & Mason, 2015). Dexmedetomidine-induced suppression of sinoatrial node firing by vagomimetic action can result in a variety of arrhythmias, including junctional escape rhythms, whilst cases of asystole from sinus arrest have also been reported (Scheinin et al., 1998). The adverse hemodynamic consequences of dexmedetomidine administration are usually easily treated (Dawes et al., 2014), however this may not apply to patients with pulmonary hypertension (Nathan et al., 2014).

As dexmedetomidine is predominantly used as an anesthetic adjuvant in clinical practice, it requires administration of additional agents in order to achieve an adequate surgical plane. Studies investigating the sedative effects of dexmedetomidine often involve the co-administration of adjunctive sedatives (Mason et al., 2008; Heard et al., 2008; Tosun et al., 2006; Hammer et al., 2009). Despite the co-administration of dexmedetomidine with numerous adjunctive agents, undersedation has been documented in up to one-third of pediatric patients (Carney et al., 2013). The facilitated arousal associated with dexmedetomidine administration may be advantageous in cooperative adults, however this may necessitate the use of higher doses of dexmedetomidine or addition of a combination of sedative adjuvants, including midazolam, propofol and ketamine, in order to achieve pediatric procedural sedation (Mason et al., 2008). However, it is important to note that conflicting results exist regarding the sedative efficacy of dexmedetomidine in conjunction with sedative adjuncts, with smaller pediatric critical care studies indicating that adequate sedation is

achieved in >90% of cases (Hosokawa et al., 2010; Chrysostomou et al., 2006; Walker et al., 2006). Overall, the necessity for adjunctive agents to be co-administered with dexmedetomidine is a potentially important clinical limitation which, in addition, may also hinder its neuroprotective effects when used in further combination with halogenated anesthetics.

7.2. Xenon

Whilst xenon has been described as the ideal anesthetic agent because of its rapidity of onset/offset and its lack of biotransformation (Bein et al., 2007), it does have limitations. These limitations are principally due to its lack of potency, with a MAC of up to 71% in adults (Goto et al., 2000). Considering the nature of other gaseous anesthetics, it is believed that the MAC of xenon is also expected to be higher in children than in adults, rendering xenon less effective in children. This would consequently limit dose administration and the inspired oxygen concentration; this is particularly important as children cannot tolerate low oxygen concentrations during surgery. Due to its high MAC, its MAC multiple that can be administered is limited, which, in combination with its reduced solubility, particularly reduces xenon's effectiveness in children with cyanotic congenital heart defects (Coté et al., 2013). Ultimately, xenon can rarely be used as a sole agent for general anesthesia under normobaric conditions, although it still maintains its capacity for neuroprotection at sub-anesthetic concentrations (Devroe et al., 2015).

Additionally, because xenon is denser than air, airway pressure will inevitably rise and, therefore, its effects may be confused with other more sinister causes, including pulmonary edema (Bedi et al., 2002). Like many other general anesthetics, xenon use is associated with a notable increase in nausea and vomiting (Schaefer et al., 2015; Coburn et al., 2008). Regarding hemodynamics, the only consistent change is a decrease in heart rate (Coburn et al., 2005).

Currently, xenon's widespread clinical application is also limited by high manufacturing costs, owing to its rarity in the atmosphere. Further investigation of potential methods to reduce these costs, such as closed-circuit xenon delivery systems, are certainly warranted.

8. Conclusions

Dexmedetomidine and xenon have been found to confer significant neuroprotection in preclinical studies, predominantly exerting their effects *via* upregulation of the α2A-adrenoceptor and downregulation of NMDA-receptor signaling, respectively, and favorably modulating the ratio of pro-apoptotic to anti-apoptotic proteins.

Preclinical studies demonstrate the ability for both agents to significantly reduce neuroinflammation and neurodegeneration following neurological insult, including perinatal asphyxia and anesthetic-induced neurotoxicity, whilst also having minimal fetotoxic effects. Paradoxically, whilst there is significant preclinical evidence suggesting the neurotoxicity of traditional anesthetics, including nitrous oxide and isoflurane, these agents still remain an important part of any standard anesthetic regimen, although the FDA have recently issued a warning regarding its use in patients under the age of three years. In contrast, despite the significant neuroprotection conferred by dexmedetomidine and xenon in preclinical studies, too few clinical trials have been conducted to confirm these benefits to date. It is important to note that confounding results suggest that both dexmedetomidine and xenon may possess some inherently neurotoxic effects. Further preclinical and well-powered clinical trials are warranted in order to elucidate the reasons for these confounding results, as well as to ascertain the precise short- and long-term effects of dexmedetomidine and xenon on the developing brain.

Conflict of interests

Dr. Ma has received consultancy fees from AbbVie, USA, and Air Liquide, Paris, France and he is also on the Scientific Advisory board of Nobilis Therapeutics, USA. Dr. Maze was a co-applicant for an issued patent regarding the use of dexmedetomidine for sedation. Stanford University assigned the rights to the patent to Farmos for $250,000, which Dr. Maze's laboratory received between 1988 and 1992. Dr. Maze has not received any royalty payments for sales of dexmedetomidine. Dr. Maze is a co-founder of NeuroproteXeon, a spin-out company from Imperial College London that intends to use xenon for neuroprotection. Dr. Maze received founders equity and has received stock options, which he has not exercised. Dr. Maze receives no payment from NeuroproteXeon. Dr. Sanders has received consultancy fees from Air Liquide, Paris, France concerning the development of medical gases and received speaker fees (>2 years hence) from Orion and Hospira concerning the use of alpha2 agonists.

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