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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

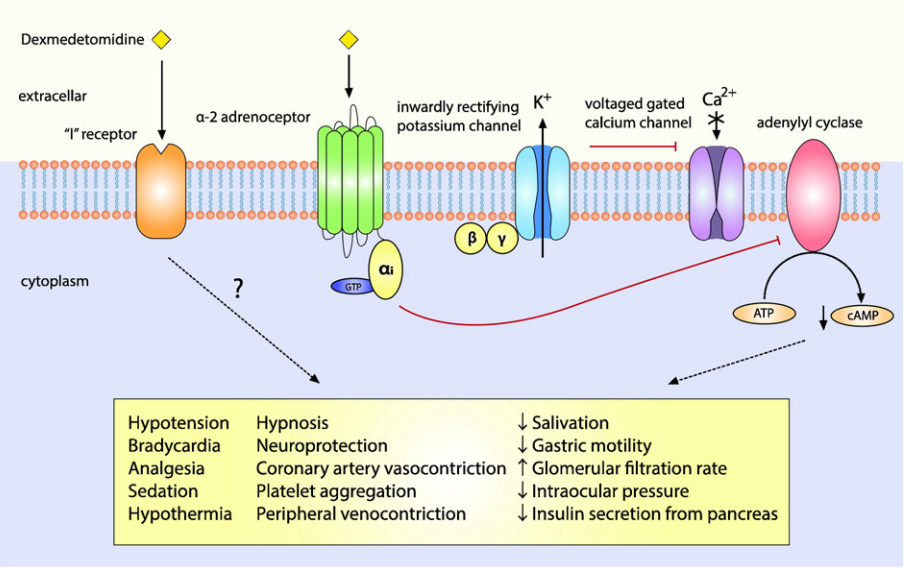

Fig. 1. The mechanism of action of dexmedetomidine. Dexmedetomidine is an agonist of the α-2 adrenoceptor, a transmembrane G-protein coupled receptor. Activation of the α-2 adrenoceptor inhibits adenylyl cyclase, which causes an intracellular decrease of cAMP. This leads to a series of cellular events 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.