Review Article

Dexmedetomidine Mechanism of Action: an Update

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Abstract

Dexmedetomidine is selective agonist for α2 receptors in the central nervous system and other organs. At present, it is used as a sedative and analgesic medicine after operations. Several studies have provided evidence for new mechanism of action of dexmedetomidine. Here we reviewed the current understanding about dexmedetomidine mechanism of action involved in neuroprotection and ischemia-reperfusion injuries.

Keywords: Dexmedetomidine, neuroprotection, reperfusion injury

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Introduction

Dexmedetomidine (PRECEDEX) is an imidazole derivative that is a highly selective α2 receptor agonist. Activation of the α2 adrenergic receptors by dexmedetomidine leads to both sedation and analgesia; with negligible respiratory and cardiovascular side effects (1). Fresh experiments have provided evidence about neuroprotective properties of dexmedetomidine which can attenuate delirium, preserve sleep architecture and preserve ventilatory drive (2,3). Beyond its effects in the central nervous system, recent studies have shown efficacy of dexmedetomidine against ischemia-reperfusion injury, and against injuries following organ transplantation (4, 5).

α 2 receptor

Dexmedetomidine is highly selective for α 2 receptors. Analgesic effects of dexmedetomidine are achieved through negative feedback control found at the presynaptic level of autonomic function and in some cases in sensory neurons. Dexmedetomidine diminishes α 2 activation with release of norepinephrine from these nerve endings and other co-transmitters which are important in signal transduction (6, 7). Presynaptic that respond to the primary transmitter substance released by nerve ending are called auto-receptors (1). α 2 belongs to the family of G protein-coupled receptors (GPCRs). GPCRs are coupled by G proteins to the various effector proteins including phospholipase C (PLC) and adenylyl cyclase (AC) whose activities are regulated by those receptors. G protein is a heterotrimer consisting of α, β, and γ subunits. GPCR activation causes production of guanosine triphosphate (GTP) from guanosine diphosphate (GDP). GTP binds to α subunit and causes dissociation from two subunits. The activated GTP-bound α subunit then regulates the activity of AC. α 2 receptors inhibit adenylyl cyclase activity and cause decrease of cyclic adenosine monophosphate (cAMP) levels (8, 9). α 2–mediated inhibition of adenylyl cyclase use other signaling pathways, including

regulation of ion channel activities and the activities of important enzymes involved in signal transduction. In addition to CNS, receptors for α2 are found platelets, the liver, pancreas, kidney, eye and heart. From an anesthesiologist point of view, neuronal hyperpolarization is a key element in the mechanism of action of dexmedetomidine and is achieved by efflux of potassium and suppression of calcium entry. Loss of intracellular potassium and inhibition of calcium entry suppress neuronal firing and can inhibit signal transduction (10, 11).

Dexmedetomidine and neuroprotection

There is an increasing concern regarding the risk of anesthetic-induced developmental neurotoxicity (AIDN) in children. Numerous studies in animals have shown that general anesthetic agents not only induce neuroapoptosis, but also affect other neurodevelopmental processes in the developing brain. Anesthetic exposure induces apoptosis and neurodegeneration in a dose and time-dependent fashion (12). In the developing brain, especially during synaptogenesis, the intracellular concentration of Cl^- is high. Activation of GABA A receptor results in Cl^- efflux and depolarization of the neuron. Depolarization mediates rise in intracellular calcium concentration, which reaches levels that can contribute to neuronal injury (13). Calcium overload triggers widespread apoptotic cell death in developing brain and eventually result in long-term neurobehavioral impairment (14). The mechanism of cell death triggered by anesthetic drugs involves translocation of Bax protein to the mitochondrial membranes, where it disrupts membrane permeability, allowing extra-mitochondrial leakage of cytochrome c, followed by a sequence of changes culminating in activation of caspase-3 (13,14). Dexmedetomidine neuroprotection appears to involve a decrease in caspase 3 levels, and reversal of isoflurane-induced decrease in anti-apoptotic Bcl-1, pERK1, and pERK2 protein expression in vivo (15). Neuro-inflammatory mediators such as cytokines may be involved in a number of key steps in the pathological cascade of events leading to anesthetic-induced neuronal injury. Anesthesia can induce cytokines release in the central nervous system, leading to deleterious neurodevelopmental effect. A study by Laudenbach showed that dexmedetomidine exhibited dose-dependent protection against brain matter loss in vivo and improved the neurologic functional deficit induced by the hypoxic-ischemic insult by α2 activation (16). Another study by Tung revealed dexmedetomidine attenuates neuronal injury induced by maternal propofol anesthesia in the fetal brains, providing neurocognitive protection in the offspring rats (17). Anesthetic agents (e.g., isoflurane, propofol) may cause neurodegeneration in the developing brains and impair animals' learning ability. In that study, administration of DEX significantly inhibited propofol-induced caspase-3 activation and microglial response in the fetal brains showing anti-apoptotic effects of dexmedetomidine. On the other hand, the recent studies considering the effects of anesthetic drugs on processed electroencephalogram show that dexmedetomidine has the most similar pattern with normal sleep (18,19). These studies suggest that based on more sophisticated a clinical study considering the EEG patterns, dexmedetomidine has much more favorable than other anesthetic agents. Add to this point, the neuroprotective effects of dexmedetomidine which is associated with the least amount of neuroapoptosis in developing brain; which is discussed in other parts of the manuscript.

Dexmedetomidine and ischemia-reperfusion (I/R) injury

During reperfusion several important substances are released. Heat shock proteins (HSP) can propagate inflammatory responses possible through toll-like receptor 4 (TLR4). Oxidants activate a signal transduction cascade that may engage the cell-death pathway and provoke apoptosis. These factors contribute to development of reperfusion injury (20). Continued ischemia causes cellular accumulation of Ca^{2+} and generation of oxygen free radicals. Free radicals can directly damage mitochondria and subsequently lead to interruption in ATP synthesis and cell death (21). Kip's work

showed that dexmedetomidine caused levels of catalase (CAT) and glutathione-S-transferase anti-oxidant enzymes, and malondialdehyde (MDA) to decrease and reduced I/R injury of lungs in rat (22). In addition, Yushitimioi's study demonstrated that dexmedetomidine reduced the incidence of reperfusion-induced ventricular arrhythmias in pigs (23). The inhibitory effect of DEX on the production of tumor necrosis factor-α (TNF-α) and interleukin IL-6 following endotoxin injection is noteworthy (24). DEX induces apoptosis of neutrophils and inhibits superoxide production by neutrophils in a dose dependent manner (25). A fresh experiment by Yao showed that pre-treatment with dexmedetomidine reduced kidney pathological injury, TLR4 expression, and cytokine production following orthotopic autologous liver transplantation (OALT) in rats (26).

Conclusion

Dexmedetomidine is able to reduce neuroapoptosis and neurodegeneration by its unique mechanism of action which varies extensively from its known sedative and analgesic effects. In addition, it has beneficial effects against I/R injuries

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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