## Review Article

# Dexmedetomidine in Neurocritical Care

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## Abstract

Early and appropriate management of brain insults has significantly reduced patient morbidity and mortality. Neuromonitoring, neuroprotection, and secondary brain injury prevention are the essential principles of brain injury management.

In this literature review, we have elaborated on the neuroprotective role of dexmedetomidine (DEX), predominantly in different animal models of brain insults and reports in patients cared for in a neurocritical care setting. We undertook an electronic literature search of articles published in English before July 2019. This search resulted in the inclusion of 59 studies from medical databanks such as PubMed, Scopus, EBSCO, CINAHL, ISC, and the Cochrane Library. The keywords used were brain, α2 agonist, neurocritical care, and dexmedetomidine.

DEX may have a neuroprotective effect in a broad spectrum of brain pathologies such as traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), ischemic stroke, intracerebral hemorrhage (ICH), and cerebral hypoxia. However, its neuroprotective role in status epilepticus (SE) is less clear. Further animal and human studies are needed before we could consider DEX as a neuroprotective agent in this patient population. Due to its favorable properties outlined in this review, DEX could be considered a favorable sedative agent in neurocritical care settings.

**Keywords:** dexmedetomidine; Neurocritical care; Neuroprotection

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## Introduction

Brain damage is one of the main causes of disability and mortality worldwide. Apart from many pathologies and neurosurgical interventions, brain injury which is most commonly caused by blunt trauma to the head can lead to severe brain tissue damage. Consequently, some regions of the brain may undergo numerous and significant alterations in their vital functions (1).

To ameliorate these damages, prompt and appropriate management within the "therapeutic window" can be of great value to reduce long-term disability and mortality in this patient population.

The main function of neuroprotective agents in the suppression of the biochemical cascades initiated by brain injury which ultimately leads to neuronal death. These neurodegenerative mechanisms include changes in membrane ion permeability, cellular

oxidative stress, mitochondrial dysfunction, increased release of excitatory neurotransmitters (particularly glutamate), and activation of the inflammatory process. Alternation in the membrane ion permeability induces $Ca2+$ influx and this leads to mitochondrial dysfunction and ultimately accelerated cell apoptosis. Therefore, targeting oxidative stress and excitotoxicity, are considered the mainstay of neuroprotective strategies (2).

Dexmedetomidine (DEX) is a selective alpha-2 agonist with a short half-life and minimal respiratory depression. These properties have made DEX a suitable drug for the ICU and procedural sedation, as well as an adjunctive agent during general and regional anesthesia. In addition to its sedative, anxiolytic, analgesic, and sympatholytic effects (3, 4). DEX has demonstrated neuroprotective properties (5). Evidence from in vitro and in vivo studies have demonstrated the neuroprotective effects of DEX against injury caused by inflammation, traumatic brain injury, ischemia-reperfusion, hypoxia, and seizure. Cellular effects, mediated by the signaling pathways other than through the DEX's α2-adrenoceptors have also been reported, conferring its neuroprotection which has been observed in different in vitro and in vivo studies (6,7), (Figure 1).

In this review, we discuss the cellular non-α2-adrenoceptor-mediated effects of DEX and its implication for neuroprotection.

## Method of Study

We carried out an electronic literature search among articles published in the English language before July 2019. Related publications were retrieved from PubMed, Scopus, EBSCO, CINAHL, ISC, and the Cochrane Library using keywords including the brain, α2 agonist, neurocritical care, and dexmedetomidine.

## Results

**Neuroprotective effects of DEX in traumatic brain injury (TBI):** Traumatic brain injury (TBI) is a major public health problem throughout the world. Due to the complexity of symptoms and often unfavorable outcome observed in TBI, effective management strategies are of paramount importance. The main TBI management guidelines focus on intracranial pressure

(ICP), cerebral perfusion pressure (CPP), mean arterial pressure (MAP), cerebral metabolic rate (CMRO2), seizure control, and other prophylactic measures (9, 10).

A recent study has indicated that TBI inducing a complex sequence of pathophysiological changes that lead to neuronal death, increase lesion volume, inflammation, and microglial activation. These changes result in neurological deficits and cognitive-motor dysfunction (10). Some studies have shown neuronal recovery facilitated by agents such as DEX, after brain injury (11). Besides, experimental studies have demonstrated the neuroprotective effects of DEX in rats following TBI. In an in vivo study on the murine model of TBI, researchers exposed mice to varying concentrations of DEX (1, 10, or 100 µg/kg bodyweight) and assessed cell death in the cortex and the hippocampus after 1 hour and 12 hours. They found the administration of DEX at the dose of 100 µg/kg reduced cell death and also reduced neuro-axonal injury and synaptic degeneration in their animal model of TBI (12).

Brain edema, a specific characteristic of TBI, classified as vasogenic or cytotoxic results from an increase in brain blood barrier (BBB) permeability due to the release of inflammatory and vasoactive mediators (13). The effects of DEX administration on brain edema reduction has been evaluated in the rat model of TBI.

In the Shen et al. animal study of a weight drop rat model, injection of 15 µg/kg DEX two hours after TBI, led to reduced modified neurological severity score (mNSS), reduced cerebral water content, and expression of autophagy proteins (LC3zsz). In their model, although the expression of inflammatory mediators such as tumor necrosis factor-alpha (TNF-a), interleukin-1β - (IL-1β), interferon-γ (INF-γ), interleukin-6 (IL-6) decreased, there was an increased expression of tight junction proteins (ZO-1 and Claudin-5) and PI3K/Akt/mTOR. It has been demonstrated that the PI3K/Akt signaling pathway plays important role in the modulation of inflammatory pathways, cell survival, and metabolic function. Besides, mTOR is a serine/threonine kinase that has a central role in the modulation of autophagy. The results of this study showed that pretreatment with DEX led to PI3K/Akt/mTOR signaling activation in the brain
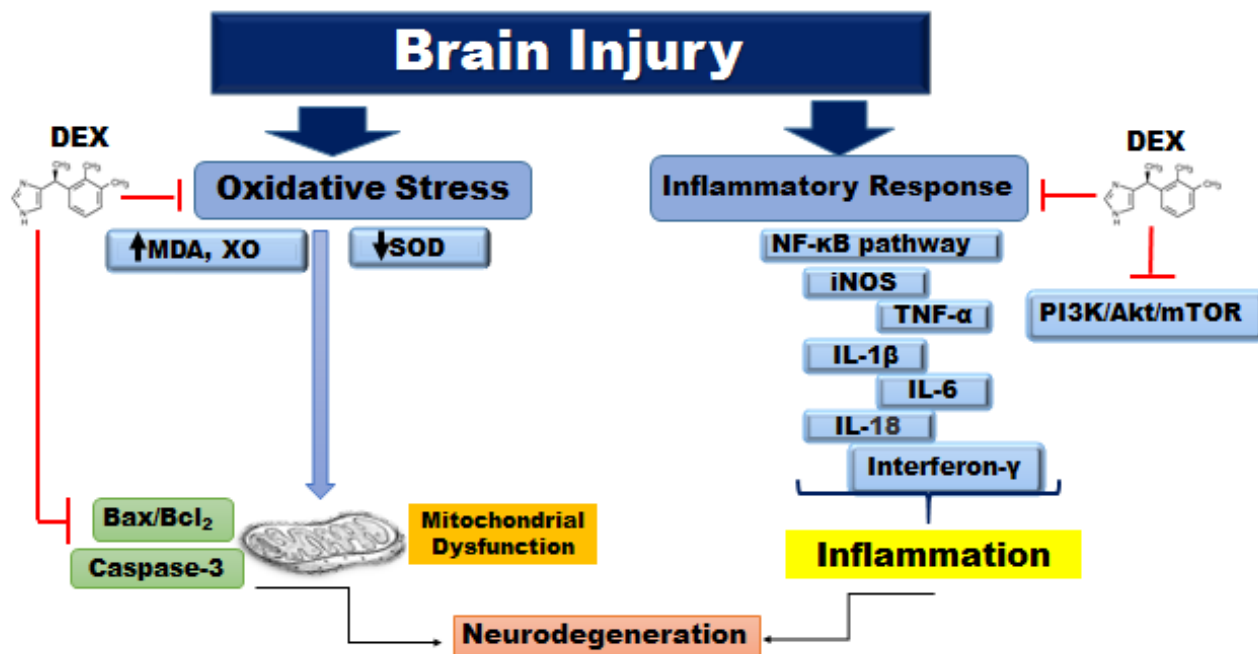
**Figure 1.** Schematic diagram showing the mechanism action of DEX in brain injury.

areas of the rat following TBI (14).

In another study administration of DEX alleviated inflammation induced by TBI. The mechanisms underlying DEX's action following the induction of TBI were increased expression of the apoptotic speck-containing protein (ASC), activation of caspase1, and processing of IL-1β and IL-18 and nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3(NLRP3) signaling These findings suggested that NLRP3-inflammasome plays a key role in the inflammatory process following TBI and might be a target for treatment (15).

DEX can inhibit stress response reactions and maintain stable cardiovascular and respiratory function (16). Tanget et al reported patients with severe TBI (GCS = 6) who had a history of chronic alcohol abuse. Theses patient received an infusion of DEX 0.5 mcg/kg/h titrated ultimately to 1.5 mcg/kg/h for 8 days. They concluded that DEX has an anxiolytic effect in this patient population. (17). The neuroprotective effect of DEX decreases the state of hyperarousal via central α2-receptors activity in the CNS. Furthermore, DEX acts on the differential GABA receptor and have beneficial anxiolytic effects (18).

**DEX in Subarachnoid Hemorrhage (SAH):** Subarachnoid hemorrhage (SAH) is bleeding in the subarachnoid space between the pial and arachnoid membranes. It has been demonstrated that structural changes such as vasospasm and hyperplasia of the arterial walls can complicate SAH (19).

Ayoglu and colleagues studied the efficacy of two doses of DEX (5 and 10 µg/kg) 1 and 24 hours after SAH, on vasospasm and oxidative stress in rats. They found that malondialdehyde (MDA) and mean wall thickness (MWT) decreased in the treatment group. Also, MDA levels and MWT and proliferating cell nuclear antigen (PCNA) expression were lower in the treatment group (10 µg/kg). These results suggested that pretreatment with DEX in a dose-dependent fashion (10 µg/kg) leads to reducing oxidative stress and vasospasm in the rats' model of SAH (20).

Another study investigated the efficacy of DEX (5 µg/kg/h) for 2 hours and 48 hours after SAH, on the hippocampus vasospasm and evaluated the biochemical markers such as MDA levels, the activity of XO (xanthine oxidase), and SOD (superoxide

dismutase) in rabbits. Administration of DEX led to decreased MDA levels and XO activity and increased SOD activity, suggesting attenuation of vasospasm in the hippocampus of their rabbit model of SAH (5).

Song and his colleagues investigated treatment with DEX on vasospasm and measured related biomarkers such as IL-6 in the SAH model of rats. They found a correlation between IL-6 levels and the occurrence of vasospasm in their SAH animal model (21).

Besides, DEX ameliorated vasospasm significantly and improved neurological outcomes in rat models of SAH which was thought to occur by reducing IL-6 levels in their CSF (22). In another rats' model of SAH, Li et al. showed higher doses of DEX (100 µg/kg body weight) compared to the lower doses (10 and 50 µg/kg body weight) resulted in better neurological scores, reduce subarachnoid hemorrhage, lesser cerebral edema and more reduction in the inflammatory interleukins such as IL-1β, IL-6, and TNF-α (23).

Yin and colleagues examined the neuroprotective effect of DEX in the early brain injury (EBI) after SAH and investigated its mechanism of action. They found that administration of DEX reduced neurological deficits, attenuated brain tissue edema, decreased the permeability of the blood-brain barrier (BBB) and the level of IL-1β, IL-6, and TNF-α (24). DEX also reduced cell apoptosis at 24 hours after SAH in rats. Particularly, it inhibited toll-like receptor 4 (TLR4)/nuclear factor-κB (NF- κB) [(TLR4/NF-κB)] signaling and NLRP3 inflammasome activation. It has been demonstrated that the TLR4/NF-κB signaling plays an important role in the release of IL-1β, IL-6, and TNF-α in EBI after SAH. The accelerated release of these inflammatory markers led to BBB disruption and cell apoptosis (24).

It seems that the neuroprotective effects of DEX in the rats' model of subarachnoid hemorrhage may be mediated in part through the extracellular signal-regulated kinase (ERK) (25). In a retrospective review by Okazaki and colleagues, the administration of DEX in the first 24h after admission was associated with favorable neurological outcomes in patients with SAH (26).

In conclusion, experimental studies, predominantly in animal models of SAH, have shown to improve neurological outcome.

DEX in Ischemic Stroke: Prior studies have reported the neuroprotective effect of DEX in cerebral ischemia. In vitro evidence suggests that DEX plays an important role in the process of ischemic preconditioning in hippocampal slices exposed to oxygen and glucose deprivation (OGD); this may be closely linked to increased phosphorylation of focal adhesion kinase (FAK) and pro-caspase-3 (27). Treatment with low dose DEX before and following the induction of cerebral ischemia prevented delayed neuronal cell death in the hippocampal CA3 region and dentate hilus of the gerbil, which is thought to occur by inhibiting the release of catecholamines (28).

Goyagi and colleagues investigated the effect of co-administration of lidocaine and DEX in rats following forebrain ischemia. They examined neurological function scores, counted the ischemic cells, and measured levels of extracellular glutamate and norepinephrine concentration in CA1 of the hippocampus. The results showed that co-administration of lidocaine and DEX in rats decreased the neurological deficit and ischemic cells in forebrain ischemia (29). Besides, preconditioning with DEX reduced permeability of the blood-spinal cord barrier (BSCB) in spinal cord ischemia-reperfusion injury in rats through inhibition of matrix metalloproteinase-9 (MMP-9), and enhanced the binding of angiopoietin-1 (Ang1) to Tie2 receptor in endothelial cells (30).

In recent years, accumulating reports have indicated neuroinflammation to play a key role in cerebral ischemia. Some studies have shown that DEX possesses a potent anti-inflammatory effect via inhibition of inflammatory cytokines and mediators (31, 32).

Jiang and colleagues demonstrated the protective effects of DEX on the experimental craniocerebral injury in rats via decrease TNF-α and IL-2 levels (33). DEX has anti-inflammatory action through the inhibition of the TLR-4/NF-κB and NF-κB pathway in ischemia-reperfusion injury in rats resulting in improved neurological deficit (34). Other studies showed DEX to attenuate significantly the damage to rat brains after Ischemia-reperfusion evaluated by NDS scores (vision, cognition, corneal reflex, m¬otor activity and seizure episodes with scores of 0 = normal and 100 = brain death). Their

results showed that treatment with DEX decreased the neurological deficit, NDS scores, S100B, and MDA levels and inhibited the expression of intracellular adhesion molecule-1 (ICAM-1) and NF- κB (35). It has also been reported that DEX increases the ratio of anti-apoptotic to pro-apoptotic factors attenuating apoptosis via inhibiting activation of its intrinsic signaling pathways (36).

**DEX and Intracerebral hemorrhage (ICH):** Cerebral hemorrhage may result in irreversible loss of functions of the nervous system. Learning and memory deficits are among the most common sequelae of ICH (37, 38). Some of the mechanisms underlying the neuronal loss of function are via decreased expression of brain-derived neurotrophic factor (BDNF) and Neuroglobin (NGB) in the brain (39).

Hwang et al. examined the effects of DEX on learning and spatial memory and apoptosis of neurons in the hippocampus after the induction of ICH in rats. The results showed DEX administration in ICH to improve learning and spatial memory with a better histopathological outcome via suppressing cell apoptosis and enhancing neuronal BDNF and TrkB gene expression in rats (40).

**DEX and Status Epilepticus (SE):** Status epilepticus (SE) is a medical emergency that can result in permanent neurobiological damage and severely affect cognitive abilities. Besides, SE patients show depression, anxiety, and other signs of mental disorders, which significantly diminish the quality of patients' life (41, 42). Some studies have shown that SE induced a range of morphological and physiological changes in the brain, such as neurogenesis, synaptogenesis, imbalance of excitatory-inhibitory signals, and neuroinflammation (43–45).

In experimental studies, pretreatment with DEX (3/μg/kg, subcutaneously) suppressed epileptic activity and neuronal damage of the principal cell layers of the hippocampus in the Kainic acid (KA) model of status epilepticus in rats (46). It has been demonstrated that DEX could increase the seizure threshold in the cocaine model of seizure in rats by reducing the response of the extracellular dopaminergic neurotransmitter to cocaine (47).

In another animal study, investigators have shown that DEX has an anticonvulsant effect on the seizures induced by nerve agents in rats. Wang et al.

reported that DEX effectively reduced the frequency and duration of seizures and diminished the level of glutamate (Glu) and the ratio of malondialdehyde (MDA) and glutathione (GSH/MDA) in the hippocampus in the model of electrical stimulation of the amygdala in rats. These results demonstrated the anti-oxidative properties of DEX in seizures (48).

In another study, the efficacy of DEX was investigated regarding cognition and neuroinflammation in the hippocampus of rats, following convulsive status epilepticus (CSE). These results showed DEX to have anticonvulsant effects as evidenced by decreased seizure severity.

Also, DEX enhanced spatial cognitive function and long-term potentiation (LTP) amplitude in the CSE model of rats. DEX has also demonstrated some antioxidant effects through the reduction of serum IL-1β, TNF-α, and S-100β levels and increased BDNF levels. Immunohistochemistry results in this study showed that the expression of α7-nicotinic acetylcholine receptor (α7-nAChR) and IL-1β decreased in the hippocampus in this model of seizures (49).

Kurosawa et al. reported that DEX depresses glutamatergic transmission, but does not influence inhibitory synaptic transmission via the GABA A-receptor in the hippocampus of rats. Furthermore, type 1 and type 2 receptors of imidazoline mediated the effect of DEX on the epileptiform discharge (50). Miriski et al. showed the effects of DEX on the seizures model induced by pentylenetetrazole (PTZ) in rats. They found that treatment with DEX had a proconvulsant effect in the PTZ model of rats (51).

Other investigations regarding the effect of DEX on seizure are inconsistent with these results. For example, Halonen et al. studied the efficacy of DEX (1, 10, or 100 μg/kg intravenously) on seizure induction index (SII) during 3.5% enflurane anesthesia in cats. These findings showed that treatment with high doses of DEX (10 and 100 μg/kg) increased SII and, as a result, decreased seizure threshold during enflurane anesthesia. In clinical practice, Kubota et al. reported an infant who was sedated by DEX (0.625 μg/kg/h) during artificial ventilation and was monitored for epileptic seizures and non-epileptic abnormal movements by EEG. They observed induced epileptic activity in this infant during artificial ventilation after

the administration of DEX (52).

In the study of Talke and colleagues on five patients with uncontrollable seizures, infusion of DEX 0.5 mg/kg for 60 minutes didn't have a significant effect on intractable epileptiform discharges (53).

**DEX and Cerebral Hypoxia:** Cerebral hypoxia often occurs following ischemic shock, cardiac arrest, or complicated cardiac surgeries (54). This results in cognitive impairment, decreased motor control, seizures, and may progress to coma and brain death. It has been demonstrated that cerebral hypoxia increases the generation of reactive oxygen species (ROS) in neural tissue. Brain hypoxia requires immediate intervention to reduce the possibility of irreversible brain damage (55, 56). Experimental studies have shown the neuroprotective effect of DEX in cerebral hypoxia (57).

In vitro studies have indicated that DEX exerts protective effects on neural tissue under hypoxic conditions. DEX displayed a preconditioning effect against hypoxic injury in hippocampal slices during oxygen and glucose deprivation (OGD). Also, DEX reduced cell apoptosis in the hippocampus when administered before the induction of hypoxia (55).

It has been demonstrated that the administration of DEX decreases brain hypoxia-induced ischemia in neonatal rats. This effect may be mediated through the inhibition of inflammatory pathways in the ischemic cerebral tissues (58). Eser et al. examined the neuroprotective effect of DEX on the hippocampus and dentate gyrus following transient global cerebral ischemia/reperfusion injury in rats. The results indicated DEX to reduce MDA and NO levels, but the activities of SOD and CAT increased. Besides, the TNF-$\alpha$ level and the number of apoptotic neurons significantly decreased after treatment with DEX (56).

Another study examined the effects of DEX on neurodegeneration, biomarkers of oxidative stress, and inflammatory markers after the induction of hyperoxia in neonatal rats. The results of this study showed DEX to significantly reduce neurodegeneration in various regions of the rat's brain. DEX also restored the ratio of reduced to oxidized glutathione and attenuated the levels of malondialdehyde and downregulated IL-1$\beta$ mRNA expression and protein levels in rat's neonatal brain. DEX provided neuroprotective effects in this model, via suppression of the oxidative stress-inflammatory cytokine signaling pathways. Based on these data, DEX has been proposed to have a neuroprotective role in neonatal rat's model of hypoxia (59).

## Conclusion

In this review, we have highlighted the neuroprotective properties of DEX in different brain pathologies. The data in patients with TBI suggest DEX has neuroprotective effects through suppression of the inflammatory pathway. In patients with SAH and cerebral hypoxia, our search indicated DEX's potentials to leads to improved neurological outcomes, mediated in part through suppression of the inflammatory and oxidative pathways. In the ischemic stroke population, DEX exerts a potent anti-inflammatory property via the inhibition of inflammatory mediators and intrinsic apoptotic signaling pathways. In the ICH patients, DEX administration improved cognitive function via suppressing cell apoptosis and enhancing neuronal BDNF signaling and TrkB gene expression. However, data regarding the effects of DEX on seizure appear to be conflicting, with some studies showing heightened seizure threshold via suppression of the inflammatory and oxidative stress pathways and others indicating decreased seizure threshold by unknown mechanisms. Overall, because of its analgesic, anxiolytic, and anti-inflammatory properties, DEX can be considered a favorable sedative agent in neurocritical care settings.

## Acknowledgment

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

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