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CRITICAL CARE (SA MAYER, SECTION EDITOR)

Does Dexmedetomidine Ameliorate Postoperative Cognitive Dysfunction? A Brief Review of the Recent Literature

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Abstract

Purpose of Review Postoperative cognitive dysfunction (POCD) occurs in 20–50% of postsurgical patients with a higher prevalence in elderly patients and patients with vascular disease and heart failure. In addition, POCD has been associated with many negative outcomes, such as increased hospital length of stay, increased rates of institutionalization, and higher patient mortality. This brief review discusses select evidence suggesting an association between neuroinflammation and POCD and whether the use of dexmedetomidine, a short-acting alpha 2 agonist, may ameliorate the incidence of POCD. We review the recent evidence for neuroinflammation in POCD, dexmedetomidine's properties in reducing inflammatory-mediated brain injury, and clinical studies of dexmedetomidine and POCD.

Recent Findings There is evidence to support the anti-inflammatory and immunomodulatory effects of dexmedetomidine in animal models. Several clinical investigations have demonstrated favorable outcomes using dexmedetomidine over placebo for the reduction of postoperative delirium. Few studies have used high-quality endpoints for the assessment of POCD and no demonstrable evidence supports the use of dexmedetomidine for the prevention of POCD.

Summary While evidence exists for the neural anti-inflammatory properties of dexmedetomidine, human trials have yielded incomplete results concerning its use for the management of POCD. Dexmedetomidine may reduce acute postoperative delirium, but further studies are needed prior to recommending the use of dexmedetomidine for the direct reduction of POCD.

Keywords Dexmedetomidine · Postoperative cognitive dysfunction · Delirium · Neuroinflammation

Introduction

Postoperative cognitive dysfunction (POCD) is a condition characterized by neurocognitive deficits after surgery that may persist for weeks or months after the inciting event. Like postoperative delirium, intensive care- related (ICU) delirium, and post-ICU cognitive dysfunction, it is likely part of the spectrum of neurocognitive deficits commonly observed after general critical illness. Controversies remain concerning its true incidence; it likely ranges from 12 to 40% with elderly patients suffering from the highest risk of cognitive dysfunction [1, 2•, 3, 4]. It has been associated with negative outcomes that include increased length of stay, rates of institutionalization, and higher mortality [5–7]. Risk factors for the development of POCD include increasing age, the presence of diabetes, vascular disease, heart failure, and atrial fibrillation, and pre-existing cognitive dysfunction [8–12]. There is evidence that dexmedetomidine (Precedex™, Pfizer, New York, NY), a short-acting alpha 2 agonist first approved by the Food and Drug Administration (FDA) in 1999 for use in sedation of intensive care patients, may ameliorate the incidence of delirium and postoperative cognitive dysfunction. This review will focus on select basic science and clinical evidence to determine its efficacy in reducing POCD.

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Review

Dexmedetomidine: Clinical Pharmacology

Alpha-2 adrenoceptors are G-protein-coupled receptors that bind catecholamines and are ubiquitously found throughout

mammalian central and peripheral nervous systems. Within the peripheral nervous system, they regulate tasks such as smooth muscle vasoconstriction and peripheral nociception [13, 14]. Within the central nervous system (CNS), alpha-2 adrenoceptors, including subtypes α_{2A}, α_{2B}, and α_{2C}, are integral to the complex regulation of the noradrenergic system. Enhanced activity within the noradrenergic system increases arousal, nociception, attention, and emotion [15]. Due to its role in these cortical functions, it is an area of intense research for the treatment of neuropsychiatric, acute pain, and chronic pain disorders [16, 17]. Dexmedetomidine is a potent, highly selective agonist at the CNS pre and post-synaptic alpha-2 adrenoceptor. Inhibitory effects are exerted in the CNS with its administration, generating a dose-dependent decrease in noradrenergic, serotoninergic, and dopaminergic output [18]. Although dexmedetomidine's activity in promoting sedation are not fully understood, functional magnetic resonance imaging (fMRI) has demonstrated a high affinity for the locus coeruleus, an area of the brain associated with arousal, dense in noradrenergic innervation, and with varied efferent targets (Fig. 1). There are similar effects on downstream efferent targets of the locus coeruleus such as the thalamus and basal ganglia [19, 20]. Though locus coeruleus inhibition is enhanced on fMRI, dexmedetomidine's overall effect mimics the activity seen with volatile anesthetics [21]. In addition to its CNS sedative properties, dexmedetomidine's suppression of the central noradrenergic pathway is likely to enhance postsynaptic dorsal root ganglion-mediated analgesia [22–25].

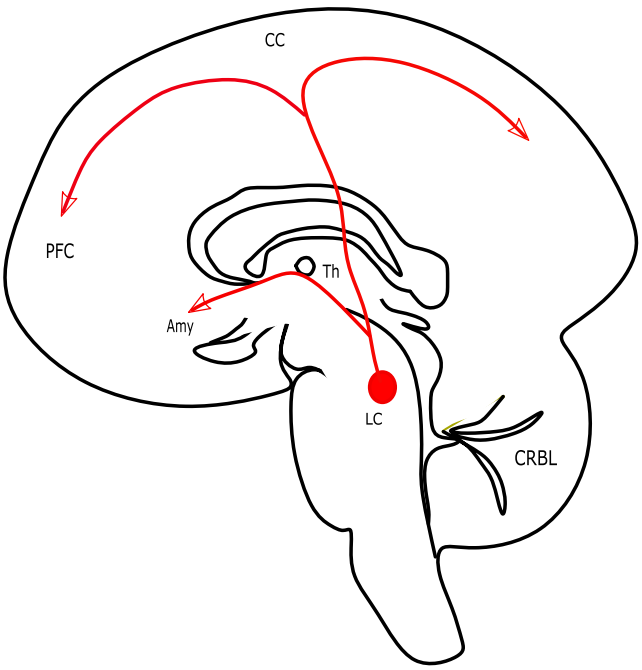

Fig. 1 Anatomy and efferent neuronal distribution of the locus coeruleus. The locus coeruleus projects widespread norepinephrine-mediated efferents to numerous targets in the midbrain and cerebral cortex. CC cerebral cortex, PFC prefrontal cortex, Th thalamus, Amy amygdala, CRBL cerebellum

Due to these unique properties, studies exploring alternative clinical applications have increased [26–31].

Neuroinflammation and Postoperative Cognitive Dysfunction

Surgical stress induces both inflammation and immune activation. This results in a localized reaction as well as a systemic cascade of inflammatory signaling molecules with generalized inflammation. Associated perioperative neuroinflammation likely plays a pivotal role in the development of POCD, among other potential factors such as accelerated neuronal aging, neuroendocrine dysregulation, circadian dysregulation, and oxidative stress [32]. Both animal and clinical models of perioperative neuroinflammation have supported this theory. Significantly elevated levels of brain interleukin-6 (IL-6), a T cell- and macrophage-derived pro-inflammatory cytokine, were observed in tandem with 1- and 2-week cognitive deficits in a surgical stress model [33]. Release of tumor necrosis factor alpha (TNFα) during the perioperative systemic inflammatory response is suspected to increase blood brain barrier permeability, promoting neuroinflammation, delirium, and subsequent POCD [34••]. Conversely, at least one study utilizing a TNFα antagonist demonstrated improved cognitive performance compared to controls after an inflammatory challenge [35]. Other studies have similarly demonstrated increased blood brain barrier permeability, providing a means for systemic inflammatory mediators to penetrate and effect neuroinflammatory changes [36, 37]. Microglia are the resident CNS macrophages and dysfunctional microglial activation likely plays a prominent role in models of POCD [38].

Clinically, perioperative neuroinflammatory changes were first suspected in numerous studies examining persistent cognitive deficits after cardiac surgery [39–41]. The role of inflammation in POCD has been further elucidated in clinical studies demonstrating increased serum levels of peripheral inflammatory markers such as C-reactive protein (CRP), S100-β, and IL-6 in patients with evidence of POCD [42–46]. A marked downregulation of human brain immune reactivity after an initial surgery-mediated systemic inflammatory response was found to be associated with persistent deleterious effects on cognition in one study [47]. This study, among others, provides more evidence that the initial systemic inflammatory response has long-lasting downstream effects on cognition after surgical intervention.

Dexmedetomidine and Neuroinflammation in Animal Models

Beyond its sedative-hypnotic effects, dexmedetomidine demonstrates far reaching modulatory effects on neuroinflammation (Fig. 2). It has demonstrated activity promoting neuroprotection against cerebral ischemia reperfusion injury by

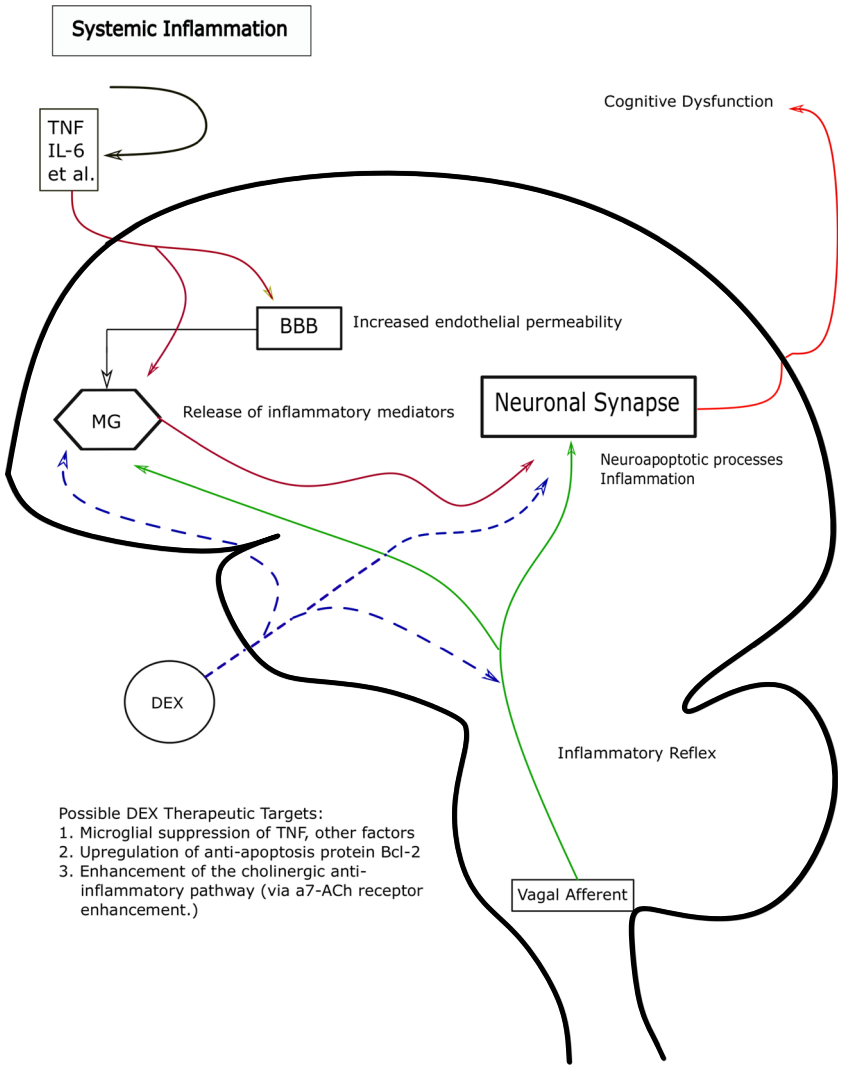

Fig. 2 Dexmedetomidine and its suspected targets in neuroinflammation. In animal models, dexmedetomidine has demonstrated far reaching effects in CNS immunomodulation. TNF tumor necrosis factor, MG microglia, BBB blood brain barrier, DEX dexmedetomidine

inhibiting expression of inflammatory cytokines via the nuclear factor-κB pathway, a key regulator of the inflammatory cascade and TNFα activation [48]. In aged rats, dexmedetomidine reduced hippocampal injury after abdominal surgery by enhancing upregulation of the anti-apoptosis protein Bcl-2 in tandem with downregulation of pro-apoptotic factors Fas, caspase-8, and caspase-9 [49]. The protective anti-inflammatory effect was only observed in animals that received concurrent administration of dexmedetomidine rather than after the inciting event [50••]. The process by which dexmedetomidine exerts these anti-inflammatory effects are complex. Dexmedetomidine, after vagotomy in a tibial fracture animal model, failed to exert its anti-inflammatory properties in the CNS. The cholinergic anti-inflammatory pathway is dependent on preserved vagal tone and its normal function is likely crucial to dexmedetomidine's beneficial modulation of neuroinflammation [51]. Dexmedetomidine's enhancement of the cholinergic anti-inflammatory pathway via α7-nicotinic-acetylcholine receptor mechanisms has been observed elsewhere [52]. In addition, there has been much scrutiny of the role played by microglia within the neuroinflammatory model. It plays an integral role in the pro- and anti-inflammatory cascade [53]. Dexmedetomidine suppresses microglia-mediated release of TNFα, nitric oxide, interleukin 1β, monocyte chemoattractant protein-1 (MCP-1), prostaglandin E2, and other factors integral to the pro-inflammatory cascade [54–57]. In addition, post-synaptic α_{2A}-adrenoreceptors have been shown to enhance prefrontal cortex activity, an area that is intrinsic to regulation of attention and behavior and implicated in the pathogenesis of delirium [15, 58].

Dexmedetomidine and Postoperative Cognitive Dysfunction in Human Trials

Inferring dexmedetomidine's effectiveness in the prevention of POCD has been limited by clinical studies that have used varied diagnostic criteria and diverse neurocognitive

Table 1 A brief overview of relevant articles with associated timeframe, endpoints, and documented *p* values

Study focus	Time point(s)	Primary endpoint	*p* value
Delirium			
Xue Li et al. (2017)	POD 1–5	CAM-ICU	(0.34)
Liu Y et al. (2016)	POD 0–7	CAM	(< 0.05)
Deiner S et al. (2017)	POD 0–5	CAM, MMSE, MDAS	(0.77)
Su X et al. (2016)	POD 0–7	CAM-ICU	(< 0.05)
Li X et al. (2017)	POD 0–5	CAM-ICU	(0.34)
Postoperative cognitive dysfunction			
Zhou C et al. (2016) [meta-analysis]	POD 0	MMSE	(< 0.05)*
	POD 1	MMSE	(< 0.05)*
Man Y et al. (2015) [meta-analysis]	POD 0–7	MMSE	(< 0.05)*
Deiner S et al. (2017)	POD 90, 180	ADC-UDS, MMSE	ns
Li X et al. (2017)	POD 6	MMSE	(0.83)

*In patients aged > 60 years old

MMSE mini-mental state examination, *POD* postoperative day, *MDAS* Memorial Delirium Assessment Scale, *ADC-UDS* Alzheimer's Disease Centers-Uniform Data Set, *ns* not significant

endpoints (Table 1). In a meta-analysis of 13 randomized controlled studies utilizing the endpoint of the mini-mental state examination (MMSE) on postoperative day 1, dexmedetomidine did confer statistical superiority to placebo in elderly patients [59]. The conclusion drawn by this analysis is limited by the early time period of testing (postoperative day one) and use of the MMSE, which has demonstrated unacceptably high dementia misclassification in patients with increasing age, educational limitations, and cultural differences [60]. A second meta-analysis also favored using dexmedetomidine for improved early postoperative MMSE performance in patients aged greater than 60 years old [61]. Similarly, this meta-analysis was limited by a wide range in the timing of neurocognitive testing making it difficult to separate features of delirium and POCD. Interestingly, this analysis found no differences between groups in studies that used neurocognitive instruments other than the MMSE. In the most comprehensive examination of dexmedetomidine for the treatment of delirium and POCD, a recent multicenter prospective trial (404 patients) examined the endpoints of postoperative delirium and 30-day and 60-day POCD in non-cardiac surgery. This study was not able to demonstrate a benefit to the use of dexmedetomidine in any of these endpoints and the study was prematurely terminated for futility [62••]. Endpoints utilized included the MMSE as well as the more comprehensive Alzheimer's Disease Centers' Uniform Data Set which has improved sensitivity for mild cognitive impairment and dementia [63]. Dexmedetomidine did significantly reduce postoperative delirium in a non-cardiac surgery cohort of older patients assessed with the confusion assessment method (CAM) up to 7 days after surgery [64]. Of note, dexmedetomidine was administered as a low-dose infusion (0.1 mcg/kg/h) from the day of surgery through postoperative day 1. Improved confusion assessment method (CAM) performance was only observed for the first 72 h in the treatment group. In contrast, a prospective RCT study examining dexmedetomidine for the prevention of delirium in cardiac surgery did not demonstrate significance superiority to placebo on the MMSE or the CAM score [65]. This study did not assess endpoints beyond postoperative day 6 and the authors intimated that the study may have been underpowered for the primary outcome. Overall, clinical studies remain mixed concerning the benefits of dexmedetomidine for the treatment of acute postoperative delirium and demonstrate no favorable effects on time periods associated with POCD.

Conclusion

In conclusion, there is support for a neuroinflammatory role in the development of POCD. Secondly, there is modest evidence to support the concept that dexmedetomidine has anti-inflammatory properties within the CNS. Within the confines of human trials, there appears to be mixed evidence supporting the intraoperative administration of dexmedetomidine to reduce the risk of POCD. In addition, studies have been hampered by the wide variety of neurocognitive instruments and time endpoints used to quantify POCD. Postoperative delirium is a condition strongly associated with a higher incidence of POCD and there is some evidence that the use of dexmedetomidine may reduce postoperative delirium in non-cardiac populations [66, 67]. In the most comprehensive large prospective trial examining dexmedetomidine and the endpoints of delirium and POCD,

no evidence to support its use was found. At this time, we cannot recommend that the practicing anesthesiologist use dexmedetomidine as part of a balanced general anesthetic specifically for the prevention of POCD; however, there is some limited support for its use in the management of post-operative delirium. The preliminary evidence warrants further large-scale clinical studies to assess the value of dexmedetomidine in preventing delirium and POCD, particularly in at-risk subpopulations.

Compliance with Ethical Standards

Conflict of Interest Zyad J. Carr, Theodore J. Cios, Kenneth F. Potter, and John T. Swick declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major Importance

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