A Review of the Biological Mechanisms of Dexmedetomidine for Postoperative Neurocognitive Disorders

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Postoperative neurocognitive disorders are common neurological complications following surgery that are generally characterized by varying degrees of cognitive impairment. Postoperative neurocognitive disorders can exhibit as short-term postoperative delirium and/or long-term postoperative cognitive dysfunction. In addition, postoperative neurocognitive disorders may result in poor outcomes in patients, and are a leading cause of postoperative morbidity and mortality, particularly in elderly patients. Recently, there has been a heightened interest in mechanisms and clinical treatments for postoperative neurocognitive disorders. Though some influencing factors and mechanisms of postoperative neurocognitive disorders have been revealed, they remain troublesome problems in clinical departments. Dexmedetomidine is a commonly used anesthetic adjuvant that may help improve postoperative cognitive impairment, especially the conditions of a postoperative acute event (postoperative delirium, within 1 week after operation) and delayed neurocognitive recovery (postoperative cognitive dysfunction, up to 30 days). In the recent literature, dexmedetomidine has been shown to exert positive effects on cognitive impairment in clinical and animal studies, especially for postoperative neurocognitive disorders. However, not all clinical findings support this efficacy. Though some mechanisms of dexmedetomidine on postoperative neurocognitive disorders have been proposed, such as signaling pathways associated with inflammation and apoptosis, this evidence is fragmentary and disputed in the literature. Therefore, this article aims to review the potential biological mechanisms underlying dexmedetomidine’s effects on postoperative neurocognitive disorders, providing a reference for future studies.

Keywords: Cognitive Neuroscience • Dexmedetomidine • Neurogenic Inflammation • Postoperative Cognitive Complications

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Background

Postoperative neurocognitive disorders (PND) are frequent neurological complications following surgery [1-3]. PND can have short-term, long-term, and even permanent effects on patient memory, attention, information processing, language understanding, and integration of social ability [1-3]. PND can be defined as an overarching term for cognitive impairment or any change identified in the perioperative or postoperative period, and can include short-term postoperative delirium (POD) and long-term postoperative cognitive dysfunction (POCD) [1-3]. POCD is a condition characterized by neurocognitive deficits that appear after surgery and that may persist for weeks or months after the inciting event [4]. POD is an acute cognitive impairment or dementia seen within 1 week after surgery [5,6].

In addition, PND is associated with increased mortality, premature exit from employment, and negative socioeconomic consequences, particularly in elderly patients [7]. Prominent risk factors for PND include increased age, baseline cognitive impairment, and low education level [1,8]. Furthermore, type of surgery, operation duration, anesthetic agents, anesthesia modality, and unique attributes of the patient can contribute to PND [1]. A history of cerebral infarction, low SpO₂ during induction of anesthesia, and long operative duration are risk factors for the development of PND in elderly patients undergoing laparoscopic surgery [9]. PND results from a complex process involving multiple pathological mechanisms caused by various factors. Although its mechanism remains unclear, stress response and inflammation are the most studied potential mechanisms [10,11]. Neuroinflammation plays a key role in the pathogenesis of PND [10]. Surgery can trigger neuroinflammation and induce POCD [12]. The inflammatory factors or cells induced by surgery in the peripheral blood penetrate the brain and affect the central nervous system (CNS) [13]. These inflammatory factors can activate microglial cells to produce an exaggerated immune response, leading to the release of a large number of inflammatory factors [14] including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). Furthermore, peripheral immune cells that enter the brain can amplify the inflammatory response [15]. Accumulated inflammatory mediators cause reversible or irreversible damage to brain tissue, leading to degeneration of neurites and, as a consequence, cognitive dysfunction [15].

Dexmedetomidine is a highly selective α₂-adrenergic receptor agonist that can exert sedative, analgesic, and anxiolytic effects. It inhibits sympathetic activity through inhibiting central sympathetic outflow by blocking the α₂ receptors in the brainstem, thereby inhibiting the release of norepinephrine [16]. It is a sedative commonly used in the perioperative period. Dexmedetomidine decreases the need for opioids and benzodiazepines, both of which are probable causes of PND [17]. Patients sedated with dexmedetomidine can retain a near-normal natural sleep architecture and be easily awakened from sedation [18]. Studies have shown that dexmedetomidine has a positive effect on the protection of postoperative cognitive function and neuroprotective actions against brain ischemia [19].

Preclinical and clinical studies have reported the neuroprotective effects of dexmedetomidine. Dexmedetomidine was superior to placebo and other agents (such as ketamine, lidocaine, and dexamethasone) in improving PND after both cardiac and non-cardiac surgeries [20,21]. Perioperative administration of dexmedetomidine significantly improved postoperative neurocognitive function compared with saline and control anesthetic agents (mainly midazolam) in a dose-dependent manner [22-30]. Dexmedetomidine can be used for pre-induction sedation, intraoperative infusion, and postoperative analgesia. The underlying mechanisms of the influence of dexmedetomidine on PND may involve multiple stress signal transduction pathways as well as the inhibition of the inflammatory response [31-37]. Therefore, this article aims to review the potential biological mechanisms underlying the protective effect of dexmedetomidine against PND, providing a reference for future studies (Table 1).

The Effects of Dexmedetomidine on Inflammatory Cytokines Associated with PND

Inflammation is an inevitable response following surgical trauma, that can trigger cognitive function impairment [38]. Several studies have shown that peripheral inflammatory mediators [such as IL-1β, TNF-α, and interleukin-6 (IL-6)] can affect the brain through the vagus nerve pathway, directly through the blood-brain barrier or periventricular area, via production of inflammatory mediators by microglial cells, and via neural inflammatory reactions; all ultimately leading to neurodegenerative changes and cognitive function impairment [39-43]. Higher levels of IL-6 will increase neuronal damage [40]. Release of TNFα during the perioperative systemic inflammatory response is suspected to increase blood-brain barrier permeability, promoting neuroinflammation, delirium, and subsequent POCD [41]. Elderly patients are more prone to postoperative cognitive impairment, possibly because of a more severe central inflammatory reaction following peripheral immune system activation [42,43].

Dexmedetomidine can decrease the expression levels of IL-1β, TNF-α, nuclear factor kappa-B (NF-kB), B-cell lymphoma-2-associated X protein (Bax), and caspase-3 in the rat hippocampus, all of which serve to inhibit hippocampal inflammation and neuron apoptosis, and thereby protect postoperative cognitive
Table 1. Summary of the mechanisms underlying the effects of dexmedetomidine on PND.

| Study                  | Subjects (size)                          | Object                  | Target or pathway (DEX dosage and time point after treatment)                                                                 | PND type (DEX dosage and time point after treatment) |
|------------------------|------------------------------------------|-------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| Chen W, 2015 [23]      | Aged surgical patients (148)             | Serum                   | IL-6↓, TNFa↓ (0.2 μg·kg⁻¹·h⁻¹, 1 day)                                                                                       | POCD↓ (0.2 μg·kg⁻¹·h⁻¹, 1 day)                        |
| Li XT, 2018 [24]       | Elderly patients (60)                     | Serum                   | IL-6↓, S100β↓, IL-10↓ (0.3 μg·kg⁻¹·h⁻¹ and 0.6 μg·kg⁻¹·h⁻¹, 1 day, 3 days, and 7 days)                                    | POCD↓ (0.3 μg·kg⁻¹·h⁻¹ and 0.6 μg·kg⁻¹·h⁻¹, 1 day, 3 days, and 7 days) |
| Xu HY, 2017 [25]       | Elderly patients (96)                     | Serum                   | IL-6↓, CRP↓ (0.5 μg·kg⁻¹·h⁻¹, 1 day and 3 days)                                                                            | POCD↓ (0.5 μg·kg⁻¹·h⁻¹, within 1 week)               |
| Li Z, 2021 [26]        | Elderly patients (120)                    | Serum                   | Aβ↓ (0.6 μg·kg⁻¹·h⁻¹ and 0.8 μg·kg⁻¹·h⁻¹, 7 days)                                                                            | POCD↓ (0.6 μg·kg⁻¹·h⁻¹ and 0.8 μg·kg⁻¹·h⁻¹, 1 day, 3 days, and 7 days) |
| Zhao W, 2020 [27]      | Elderly patients (416)                    | Serum                   | IL-6↓, IL-10↓ (0.5 μg·kg⁻¹·h⁻¹, 1 day)                                                                                      | POCD↓ (200 ug and 400 ug, 1-3 days and 7 days)        |
| Gong Z, 2018 [30]      | Patients undergoing extracorporeal coronary artery bypass surgery (80) | Serum                   | IL-6↓ (0.5 μg·kg⁻¹·h⁻¹, 1 day)                                                                                              | POCD↓ (0.2 μg·kg⁻¹·h⁻¹, within 1 week)               |
| Naguib AN, 2013 [31]   | Children undergoing surgical repair of congenital heart disease(48) | Serum                   | IL-6↓, IL-10↓ (0.5 μg·kg⁻¹·h⁻¹, 1 day)                                                                                      |                                                     |
| Zhang Y, 2018 [35]     | Sprague-Dawley aged rats, 18-20 months old, weight 400-550 g (90) | Cerebrospinal fluid Brain tissue | Aβ↓, p-Tau↓, PSD95↑ in hippocampus and prefrontal cortex (50 μg/kg, after operation) Aβ↓, p-Tau↑, PSD95↓ in cerebrospinal fluid (50 μg/kg, after operation) | POCD↓ (50 ug/kg, 31st to 35th days after operation) |
| Endesfelder S, 2017 [36]| 6-day old Wistar rats (80)               | Brain tissue            | Transcription factors (SOX2, Tbr1/2, Prox1)↑, regulators of neuronal plasticity (Nrp1, Nrg1, Syp, and Sema3α/β)↑ (1 μg/kg and 5 μg/kg, 24 h) |                                                     |
| Li Y, 2015 [37]        | Elderly patients (120)                    | Serum                   | IL-1β↓, IL-6↓, CRP↓ (0.4 μg·kg⁻¹·h⁻¹, 6 h and 1 day)                                                                          | POCD↓ (0.4 μg·kg⁻¹·h⁻¹, 1 day)                        |
| Chen N, 2019 [43]      | Male Sprague Dawley rats, aged 18 months, weight 400-500 g (80) | Hippocampus             | IL-1β↓, TNF-α↓, NF-kB↓, activation of microglia↓ (10 μg/kg and 30 μg/kg, 1 day and 3 days)                                | POCD↓ (10 μg/kg and 30 μg/kg, 1 day and 3 days)      |
| Qian XL, 2015 [44]     | BALB/c mice (20-22 month old, weight 60-70 g) | Hippocampus             | IL-1β↓, TNF-α↓, Bax↓, caspase-3↓ (15 μg/kg and 25 μg/kg, 1 day and 3 days)                                                  | POCD↓ (15 μg/kg and 25 μg/kg, 1 day and 3 days)      |

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Table 1 continued. Summary of the mechanisms underlying the effects of dexmedetomidine on PND.

| Study          | Subjects (size)                      | Object                     | Target or pathway (DEX dosage and time point after treatment)                                                                 | PND type (DEX dosage and time point after treatment)                  |
|----------------|--------------------------------------|----------------------------|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Zhu YS, 2019 [46] | Male Sprague Dawley rats, aged 18 months, weight 500-600 g (75) | Hippocampus                | IL-1β↓, TNF-α↓ (12 μg/kg, 1 day and 3 days)                                                                                     | POCD↓ (12 μg/kg, 1 day, 3 days, and 7 days)                             |
| Bao Y, 2019 [48]  | BV2 cells                              |                            |NF-κB↓, miR-340↑, TNF-α↓, IL-6↓, IL-1β↓, IL-2↓, IL-12↓, MCP-1↓, IL-10↑ (20 μg/mL, 24 h)                                      | POCD↓ (25 μg/kg, 1 day, 3 days, and 7 days)                             |
| Zhou XY, 2020 [55] | BV2 cells, Male elderly C57BL/6 mice (15 months old, weight 30-45 g) | Bv2 cells, Hippocampus     |TNF-α↓, IL-1β↓, IL-6↓, TLR4↓, NF-κB↓ in BV2 cells (0.1 μg/mL, 24 h) TNF-α↓, IL-1β↓, IL-6↓, TLR4↓, NF-κB↓ in BV2 cells in hippocampus (25 mg/kg, 24 h) | POCD↓ (25 μg/kg, 1 day, 3 days, and 7 days)                             |
| Bao F, 2019 [61]  | HT22 cell line                        |                            |HIF-α/PKM2 pathway↓, PI3K-AKT pathway↑ (200 μM, 24 h)                                                                        | Propofol-induced neurological function impairment↓ (25 μg/kg, 25 μg/kg and 75 μg/kg, 9 weeks old) |
| Xiao Y, 2018 [62] | Male Sprague Dawley rats at 7 days of age and weighing 10-15 g | Hippocampus                |PSD95↑, PI3K/AKT pathway↑, propofol-induced neuronal damages↓ (25 μg/kg, 25 μg/kg and 75 μg/kg, 9 weeks old) propofol-induced neuronal apoptosis in the hippocampus↓ (75 μg/kg, 9 weeks old) | Propofol-induced cognitive deficits↓ (75 μg/kg, 33 days)               |
| Wang Y, 2016 [63] | Male postnatal day 7 Sprague Dawley rats weighing 12-16 g | Hippocampus                |Bax/Bcl-2↓, caspase-3↓, PI3K/AKT/GSK-3β pathway↑ (75 μg/kg, 7 days)                                                          | Propofol-induced cognitive deficits↓ (75 μg/kg, 33 days)               |
| Li Y, 2014 [64]  | 7-day-old Sprague-Dawley rat pups weighting 14-18 g | Hippocampus                |Caspase-3↓, Bcl-xl/Bad↑, AKT↑, hippocampal neuroapoptosis↓ (50 μg/kg, 75 μg/kg, and 3 doses of 25 μg/kg, 2 h)                 |                                                                        |
| Xing N, 2020 [66] | 7-day-old Sprague-Dawley rats weighing 14-18 g (105) | Hippocampus                |PSD95↑, caspase 3↓, Bax↓, miR-34a↓, aPI3K-Akt pathway↑, (25 μg/kg, 50 μg/kg, 75 μg/kg, 2 h) Propofol-induced hippocampal neurons injury↓, (from 0.01-100 μmol/L, best: 1 μmol/L, 3 h↑) |                                                                        |
| Peng M, 2019 [67] | Male Sprague-Dawley rats weighing 200-240 g | Hippocampus                |Cerebral ischemic injuries↓, GLT-1↑, Phospho-AKT/AKT↑ (1 μg/kg, 2-24 h)                                                       |                                                                        |
| Wang N, 2019 [68] | Sprague-Dawley (SD) rats, weighing 150-200 g (50) | Hippocampus                |IL-6↓, IL-8↓, TNF-α↓, PI3K/AKT/mTOR pathway↑ (4 μg/kg, after surgery)                                                        |                                                                        |
| Xiong B, 2016 [69] | 18 month-old male Sprague-Dawley rats, weighing 500-600 g (90) | Hippocampus                |Fas↓, caspase-8↓, and caspase-9↓, Bcl-2↑, hippocampal apoptosis↓ (3 μg/kg and 12 μg/kg, 1 day, 3 days and 7 days) | POCD↓ (3 μg/kg and 12 μg/kg, 1 day, 3 days and 7 days)               |
### Table 1 continued. Summary of the mechanisms underlying the effects of dexmedetomidine on PND.

| Study            | Subjects (size)                                                                 | Object | Target or pathway (DEX dosage and time point after treatment)                                                                 | PND type (DEX dosage and time point after treatment) |
|------------------|---------------------------------------------------------------------------------|--------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| Li H, 2018 [74]  | The human microglia clone 3 (HMC3) cell line                                   |        | IL-1β↓, IL-18↓ (10 µM, 24 h) c-Fos↓, NLPR3↓ (0.1 µM, 1 µM, 10 µM, 24 h)                                                   |                                                      |
| Zhu YS, 2019 [75]| Specific-pathogen free 18-month-old male Sprague-Dawley rats weighing 500-600 g (75) | Hippocampus | TNF-α↓, IL-1β↓, GABABR1↓, GABABR2↓, cAMP↑, PKA↑, p-CREB↑, BDNF↑ (12 µg/kg, 1 day and 3 days)                            |                                                      |
| Sun W, 2020 [76] | Male NIH Swiss mice, aged 9 weeks and weighing 20-24 g (64)                    | Hippocampus | miR-129↑, YAP1/JAG1 pathway↑ (24 h)                                                                                           | Cognitive impairment↓ (24 h)                         |
| Wang YL, 2021 [77]| C57BL/6j aged 18 weeks mice                                                     | Hippocampus | miR-381↑, EGR1/p53 pathway↓, hippocampal neuron apoptosis↓ (5 µg/kg, 14 days)                                               | POCD↓ (5 µg/kg, 14 days)                             |
| Wang WX, 2018 [78]| Male Sprague-Dawley rats weighing 500-600 g                                    | Hippocampus | IL-1β↓ and TNF-α↓ in plasma (3 µg/kg and 12 µg/kg, 24 h) IL-6↓, TNF-α↓, p38-MAPK↓, Phosphorylated CREB↑, PKA↑ and BDNF↑ in the hippocampus (3 µg/kg and 12 µg/kg, 24 h) | (3 µg/kg and 12 µg/kg, within 1 week)               |
| Anjum N, 2015 [86]| ASA I-II patients, scheduled for laparoscopic cholecystectomy (45)              |        | POCD↓ (0.5 µg·kg⁻¹·h⁻¹, 30 min)                                                                                             |                                                      |
| Deiner S, 2017 [87]| Elderly patients undergoing major elective noncardiac surgery (404)           |        | POD- (0.5 µg·kg⁻¹·h⁻¹, hospital stay or 5 days)                                                                             | POD- (0.5 µg·kg⁻¹·h⁻¹, 3 months and 6 months)       |
| Turan A, 2020 [88]| Patients undergoing cardiac surgery with cardiopulmonary bypass (794)         |        | POD- (0.1 µg·kg⁻¹·h⁻¹, 0.2 µg·kg⁻¹·h⁻¹, 5 days)                                                                             |                                                      |

↓ – inhibit or decrease; ↑ – enhance or increase; ‘-’ – no effects; N/A – not available. DEX – dexmedetomidine; PND – postoperative neurocognitive disorders; POCD – postoperative cognitive dysfunction; POD – postoperative delirium; IL – interleukin; TNF-α – tumor necrosis factor-α; S100β – S100 calcium binding protein B; CRP – C-reaction protein; Aβ – amyloid β-protein; p-Tau – phosphorylated microtubule associated protein Tau; PSD95 – postsynaptic density protein; SOX2 – SRY-Box transcription factor 2; Bcl-2 – B-cell lymphoma 2; MAP2 – microtubule associated protein 2; cAMP – cyclic adenosine monophosphate; CREB – cAMP-responsive element binding protein; BDNF – brain derived neurotrophic factor; Sema3a/f – semaphorin 3A and 3F; NF-kB – nuclear factor kappa-B; Bax – B-cell lymphoma 2 associated x; MCP-1 – monocyte chemoattractant protein-1; HIF-α – hypoxia inducible factor 1 subunit alpha; PKM2 – pyruvate kinase isozyme type M2; P38 – phosphoinositide-3 kinase; Akt – protein kinase B; Fas – fas cell surface death receptor; c-Fos – fos proto-oncogene; Bcl-2 – B-cell lymphoma 2; GSK-3β – glycogen synthase kinase-3β; Bax – B-cell lymphoma extra large; Bad – Bcl-2-associated death promoter; mTOR – mammalian target of rapamycin; GLT-1 – major glutamate transporter; GABABR1 – γ-Aminobutyric acid B receptor 1; GABABR2 – γ-Aminobutyric acid B receptor 2; cAMP – cyclic adenosine monophosphate; PKA – protein kinase A; CREB – responsive element binding protein; p-CREB – phosphorylated CREB; BDNF – brain derived neurotrophic factor; YAP1 – Yes-associated protein 1; JAG1 – Jagged 1; MAPK – mitogen-activated protein kinase; ASA – American Society of Anesthesiologist.
dysfunction [43,44]. Dexmedetomidine combined with etomidate has been shown to inhibit the expression of IL-17A in rats [45]. Additionally, dexmedetomidine can alleviate PND in elderly patients by reducing plasma TNF-α and IL-6 concentrations [46].

The Effects of Dexmedetomidine on Inflammatory Mediators Associated with PND

NF-κB is an important regulator of inflammation and immune response [47]. It is primarily involved in cellular stress reactions, cytokine expression, and apoptotic regulation in inflammatory cascades. Dexmedetomidine exerts anti-inflammatory effects by inducing mir-340 overexpression and reducing NF-κB levels [48]. Toll-like receptors (TLRs) can recognize pathogen-related molecules and transmit signals into the cell, activate NF-κB, promote the transcriptional synthesis of inflammatory factors (such as TNF-α, IL-1, and IL-6), and initiate the inflammatory response to fight infection [49]. TLR4 is involved in the inflammatory response, and NF-κB is an important transcription factor downstream of the TLR4 gene [50]. TLR4 regulates the transcription of multiple pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, by promoting activation of the NF-κB pathway [51]. Therefore, the TLR4/NF-κB signaling pathway is essential in the inflammatory response. Lipopolysaccharide (LPS) is a TLR4 ligand that can activate microglia to produce pro-inflammatory cytokines, thereby inducing cognitive impairment [52,53]. Therefore, LPS-induced inflammation is a commonly used model for the study of PND [54]. Pretreatment with dexmedetomidine can improve LPS-induced PND in aged mice by inhibiting the TLR4/NF-κB pathway in the hippocampus [55].

The Effects of Dexmedetomidine on Oxidative Stress Associated with PND

The stress reaction during the perioperative period includes 3 aspects: psychological stress, anesthetic stress, and surgical trauma stress. Glucocorticoid receptors are present in the frontal cortex, especially the hippocampus, which is the region most frequently selected for investigation of the mechanism by which dexmedetomidine impacts postoperative cognitive impairment [56]. Oxidative stress plays an essential role in neuronal damage and cognitive dysfunction [57].

The phosphoinositide-3 kinase (PI3K)/protein kinase B (AKT) pathway plays an important role in neuronal damage associated with PND [58-60]. Dexmedetomidine can protect hippocampal neuronal HT22 cells against apoptosis caused by isoflurane through the PI3K/AKT pathway [61]. Besides, dexmedetomidine can attenuates propofol and isoflurane-induced neuroapoptosis and juvenile cognitive deficits via the activation of the PI3K/AKT pathway in the hippocampi of young rats [62-68].

The Effects of Dexmedetomidine on Neuronal Apoptosis Associated with PND

Apoptosis of hippocampal neurons also contributes to PND [69]. In PND mice, the expression of the fas cell surface death receptor (Fas), caspase-8, and caspase-9 proteins were upregulated, and B-cell lymphoma-2 (Bcl-2) was downregulated, which exerted anti-apoptosis effects. Overexpression of relaxin-3 in trauma and emergency states is responsible for neuronal apoptosis and brain damage [70,71]. Dexmedetomidine can reduce relaxin-3, Fas, caspase-8, and caspase-9, and increase Bcl-2 in the CA1 region of the hippocampus in aged rats [69].

NLRP3 plays a critical role in the initiation of inflammation in microglia [72]. Activated NLRP3 triggers the cleavage of procaspase-1 into caspase-1, which induces the release of IL-1 and IL-18 [73]. The transcription factor fos proto-oncogene (c-Fos) can bind to the promoter region of the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) gene and positively regulate the expression of its downstream target caspase-1. Dexmedetomidine reduces PND in elderly rats by inhibiting the activation of c-Fos [74]. Besides, dexmedetomidine can alleviate PND by upregulating the cathelicidin antimicrobial peptide (cAMP)-protein kinase A (PKA)-cAMP responsive element binding protein (CREB) signaling pathway to attenuate surgical trauma-induced hippocampal inflammation through inhibiting the gamma aminobutyric acid-B receptor [75].

The miR-129/Yes-associated protein 1 (YAP1)/Jagged 1 (JAG1) and miR-381/early growth response 1 (EGR1)/p53 pathways are associated with hippocampal neuronal apoptosis, and can alleviate DNA damage, neuroinflammation, and cognitive impairment. Dexmedetomidine can activate these pathways and thereby improve PND [76,77].

Surgery and isoflurane anesthesia reduce doublecortin (DCX)-positive neurons and brain-derived neurotrophic factor (BDNF) expression, which may give rise to neurogenesis. Dexmedetomidine can prevent PND and promote neurogenesis through upregulation of BDNF and p-CREB/CREB, factors which are related to the neuronal apoptotic pathway cAMP/PKA-CREB [78].

The Effects of Dexmedetomidine on Blood–Brain Barrier Integrity During PND

The blood-brain barrier (BBB), a protective barrier between plasma and neurons, can be damaged by surgical trauma-induced systemic inflammation. Such damage is associated with cognitive dysfunction. The major facilitator superfAMILY domain-containing protein 2 (Mfsd2a) is regulated by pericytes to promote BBB integrity [79]. Mfsd2a-deficient mice demonstrate
neurological abnormalities, including ataxia [80]. Further, lipid and brain development are associated with functional maintenance. Dexmedetomidine stabilizes BBB integrity by increasing Mfsd2a expression and reducing the incidence of cognitive dysfunction after surgical trauma [81].

The Effects of Dexmedetomidine on Proteins Associated with Alzheimer’s Disease

Polymerization of the amyloid beta 42 (Aβ) protein increases intracellular calcium concentration, induces apoptosis and neurotoxicity, and mediates neuronal cell death through microtubule-associated protein Tau (Tau) phosphorylation [82]. Postsynaptic density protein (PSD95) is critically involved in synapse formation [35, 83-85]. Dexmedetomidine, which is used in aged rats during cardiopulmonary bypass, can affect the expression of Aβ, p-Tau, and PSD95 proteins in cerebrospinal fluid, hippocampus, and prefrontal cortex, and thereby protect neurological function [35]. Dexmedetomidine reduces the incidence of PND in patients receiving orthotopic liver transplantation, and its mechanism of action may be attributed to decreased Aβ and Tau levels [85].

Future Developments

Though some studies have observed protective effects of dexmedetomidine on PND, the results are controversial. Intraoperative application of dexmedetomidine may cause a delay in recovery from anesthesia [86]. A multicenter study has shown that dexmedetomidine had no better effects on PND than placebo groups in non-cardiac surgery [87]. Furthermore, perioperative use of dexmedetomidine has no benefit in cardiac surgery in terms of the postoperative complications of delirium and atrial fibrillation [88]. Thus, dexmedetomidine should not be infused to reduce atrial fibrillation or delirium in patients undergoing cardiac surgery. Besides, in the literature, cognitive function was assessed mostly on the first, third, and seventh postoperative days, and only a few studies evaluated aspects of long-term prognosis. More studies are needed that involve long-term followup and robust cognitive evaluation to confirm or refute long-term improvement (>1 week) from dexmedetomidine.

Conclusions

Early diagnosis and supportive treatment are important to improve PND outcomes. The mechanisms underlying PND involve many factors, including inflammation and stress reactions. The underlying mechanisms of dexmedetomidine on PND may involve multiple stress signal transduction pathways and inhibition of the inflammatory response. Furthermore, the neurotoxic effects of general anesthetic agents, cerebral hypoperfusion, and sleep disturbances are also associated with the development of cognitive impairment in the postoperative period. Especially in elderly patients, long-term sleep disturbance can lead to significant impairment of cognitive function. Whether these mechanisms are involved in dexmedetomidine-induced amelioration of postoperative period cognitive impairment remains to be further investigated. Although most clinical and animal experiments support the ameliorative effects of dexmedetomidine on PND, these effects are controversial, and specific mechanisms must be further investigated.

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