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Dexmedetomidine in cardiac surgery: Emphasis on interleukin-18 signaling pathway

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Abstract

Background: Dexmedetomidine (Dex), a non-opioid anesthetic and highly selective alpha2 (α2) adrenergic receptor agonist, exerts beneficial effects by mitigating inflammation and myocardial injury during cardiac surgery. These protective actions are mediated through its anti-inflammatory, anti-apoptotic, antioxidant, and anti-stress properties, as well as by the activation of the innate immune system. Notably, the immune and adrenergic systems are closely interconnected. Adrenergic receptors are expressed on both innate and adaptive immune cells, enabling them to respond directly to signals from the sympathetic nervous system.

Methods: A systematic literature search was conducted across several prominent academic databases, including PubMed, Scopus, Elsevier, and Google Scholar, from January 2015 to December 2025. To ensure focus and consistency, language restrictions were applied, limiting the included literature to English-language publications where the database functionalities permitted such filtering.

Results: Interleukin-18 (IL-18) is identified as a pro-inflammatory cytokine belonging to the interleukin-1 (IL-1) superfamily. It is produced by a variety of cell types, including macrophages, epithelial cells, T cells, neutrophils, natural killer T (NKT) cells, and B cells. Evidence suggests its involvement in the pathophysiology of several inflammatory diseases, such as ischemia/reperfusion injury, cardiac surgery complications, transplant rejection, and autoimmune disorders.

Conclusion: Dex is posited to enhance postoperative cardiac function by modulating the immune system through the attenuation of IL-18 secretion from immune cells, consequently mitigating inflammatory responses in the context of cardiac surgery. This review aims to investigate the intricate interplay between cardiac pathologies and IL-18, while also elucidating the IL-18 signaling pathways influenced by Dex in the setting of open-heart surgery.

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Highlights

What is current knowledge?

Current knowledge indicates that IL-18 is implicated in the pathophysiology of various conditions, including ischemia/reperfusion injury, cardiac surgery, transplant rejection, and autoimmune diseases. Dex has been shown to improve postoperative cardiac function by modulating the immune system, specifically by reducing IL-18 production from immune cells.

What is new here?

Novel to this context is the identification of a reciprocal interaction between cardiac diseases and IL-18 signaling, as well as the involvement of Dex-mediated IL-18 signaling pathways in the setting of open-heart surgery.

Introduction

Coronary artery bypass graft (CABG) surgery utilizing cardiopulmonary bypass (CPB) is a recognized instigator of inflammatory responses. Several factors inherent to cardiac surgery, including valvular repair procedures, anesthetic agents, cardioplegic arrest, myocardial ischemia followed by reperfusion, surgical trauma, and the extracorporeal circulation provided by the heart-lung machine, have been implicated in the elicitation of these reactions (1). Notably, the surgical context may also lead to the release of non-pathogen-derived endogenous danger signals, which can subsequently activate the innate immune system (2,3).

Furthermore, the myocardium itself acts as a source of reactive oxygen species (ROS) and inflammatory mediators, which likely contribute to the deterioration of cardiac pump function. Consequently, these inflammatory responses should be carefully considered to mitigate the incidence of postoperative complications (4). Negative outcomes following CPB surgery and the presence of organ dysfunction exhibit a strong correlation with the equilibrium between the gene expression of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), and anti-inflammatory cytokines, such as interleukin-10 (IL-10). Interleukin-18 (IL-18) stands out among various clinical and cytokine assessments as a pivotal cytokine governing this equilibrium, exhibiting notable predictive capacity for organ dysfunction and adverse prognoses subsequent to CPB. This highlights the significant role of IL-18 in cardiovascular pathologies and during cardiac surgical procedures. Initially identified as a factor that stimulates the production of interferon-gamma (IFN-γ) by inducing Type 1 helper (Th1) T cells, leading to IFN-γ release (5), IL-18 is classified within the interleukin-1 (IL-1) family and functions as a pro-inflammatory cytokine (6). The synergistic interaction between IL-18 and interleukin-12 (IL-12) stimulates the release of IFN-γ from lymphocytes. Elevated serum levels of IL-18 correlate with a reduction in the production of the anti-inflammatory cytokine IL-10 and a concomitant increase in the pro-inflammatory cytokine TNF-α. Following CPB surgery, a rise in serum IL-18 concentrations has been observed (7,8). Increased IL-18 activity may serve as a predictive biomarker for several adverse cardiac events,

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including inflammation and injury, hypertrophy, dysfunction, and extracellular matrix (ECM) remodeling (9,10).

It is further posited that IL-18 triggers lymphocyte-mediated cytotoxicity in endothelial cells. This process is hypothesized to contribute to the disruption of the glycocalyx and induce adverse effects during or immediately following CABG surgery (11). Prior research has demonstrated that IL-18, upon cleavage by nucleotide-binding domain, leucine-rich repeat-containing family, pyrin domain-containing 3 (NLRP3), exacerbates ischemia/reperfusion-induced cardiac injury and inflammation. This exacerbation occurs through the activation of the signal transducer and activator of transcription 3 (STAT3)/forkhead box protein O3 (FOXO3)/C-X-C chemokine ligand 16 (CXCL16) pathway (12).

Dex, a non-opioid anesthetic agent that selectively activates alpha2 ($\alpha 2$) adrenergic receptors, has been extensively employed in cardiac surgery (1). Furthermore, beyond its anesthetic properties, Dex exerts beneficial effects in mitigating inflammation and myocardial damage during cardiac surgical procedures. These protective roles are attributed to its anti-inflammatory, anti-apoptotic, antioxidant, and anti-stress mechanisms, as well as its capacity to activate the innate immune system (13-17). Prior research has demonstrated the potent anti-inflammatory properties of Dex in individuals undergoing cardiac surgery or experiencing cardiovascular pathologies. These anti-inflammatory effects of Dex are mediated through diverse signaling pathways, notably by suppressing the production of pro-inflammatory cytokines, such as TNF-α, IL-8, IL-1, interleukin-6 (IL-6), INF-γ, and NF-κB. Simultaneously, Dex facilitates the activation of anti-inflammatory markers, including IL-10, NK-T cells, and a shift towards a type 1 T helper (Th1): type 2 helper (Th2) T cell, … cell balance, thereby contributing to the preservation of patients' immunity (13-17). Additionally, in an in vitro model of cardiac fibroblast hypoxia/reoxygenation, Dex inhibited the activation of the NLRP3 inflammasome. The study's findings indicated that Dex significantly downregulated the expression of several pro-inflammatory cytokines and apoptosis-related proteins, including interleukin-1β (IL-1β), IL-18, TNF-α, NLRP3, caspase-1, cleaved caspase-1, and apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC). Consequently, Dex treatment mitigated cellular inflammation and apoptosis, alongside improvements in hemodynamic parameters (18).

Consequently, this review was undertaken to specifically examine the role of Dex and its interplay with the IL-18 signaling pathway in modulating the immune response following open-heart surgery.

Methods

A systematic literature review was conducted across several major databases, including PubMed, Scopus, Elsevier, and Google Scholar, from January 2015 to December 2025. The search strategy focused on preclinical studies (Both in vivo and in vitro), clinical trials, systematic reviews, meta-analyses, and literature reviews pertaining to the anti-inflammatory effects of Dex in the context of cardiac surgery and its potential relationship with the IL-18 signaling pathway within the immune system. The following keywords were employed in the English language search: “Dexmedetomidine,” “alpha2 adrenergic receptor,” “cardiac surgery,” “interleukin-18,” “inflammation,” and “sympatholytic.” Articles published in languages other than English were excluded if the database search functionalities allowed for such restrictions.

Dexmedetomidine and interlukine-18: Organization and benefits on heart diseases

Previous studies have investigated the roles of Dex and IL-18 in cardiovascular diseases. The corresponding mechanisms are presented in Figures 1 and 2. The key findings derived from these investigations are detailed below.

Interlukine-18 in heart diseases

IL-18, a member of the IL-1 cytokine family, functions as a pro-inflammatory signaling molecule. IL-18, in conjunction with IL-1, plays a role in the activation of Th1 cells (5). This pro-inflammatory cytokine is produced by a variety of cell types, including macrophages, epithelial cells, T cells, neutrophils, NK-T cells, and B cells (Figure 1). Notably, IL-18 has been implicated in the pathophysiology of several inflammatory conditions, such as ischemia/reperfusion injury, transplant rejection, and autoimmune diseases (22).

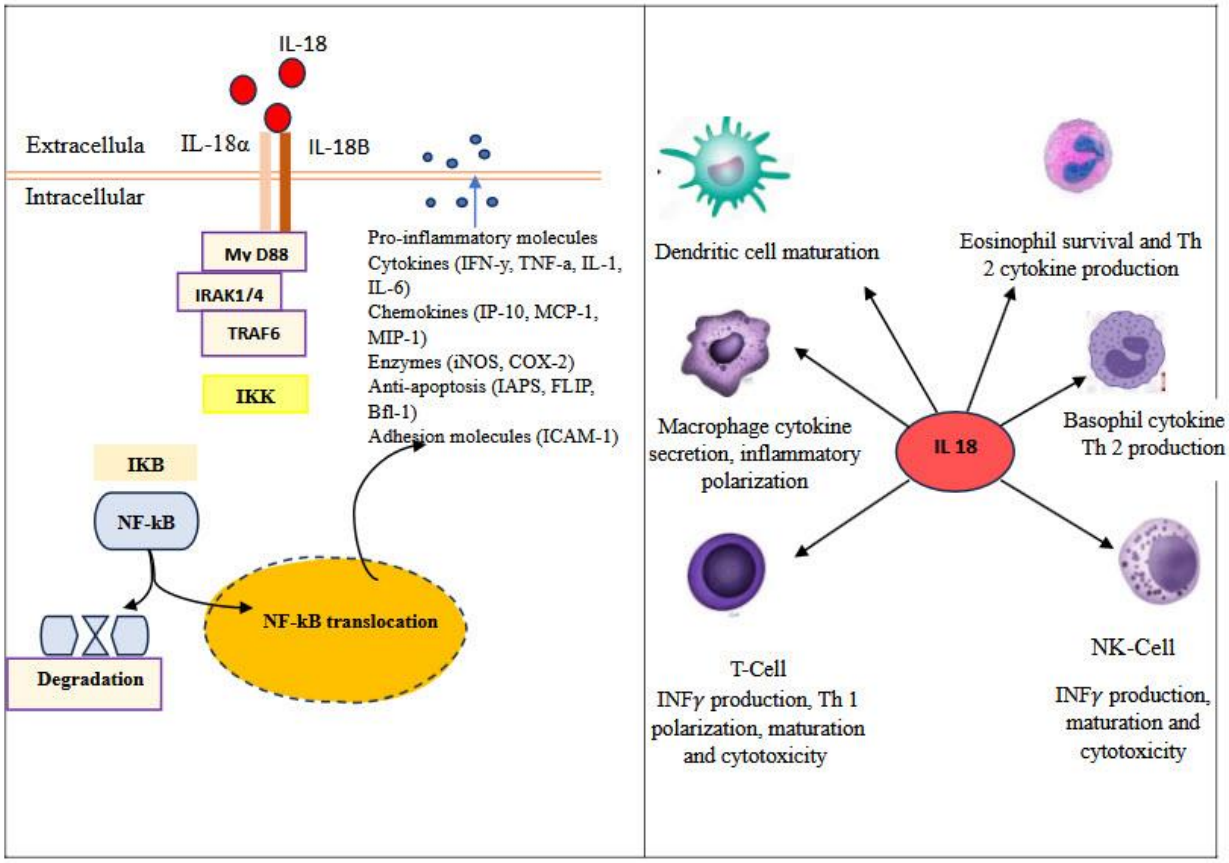

Figure 1. Interlukine-18 signaling pathways in inflammation (19,20)

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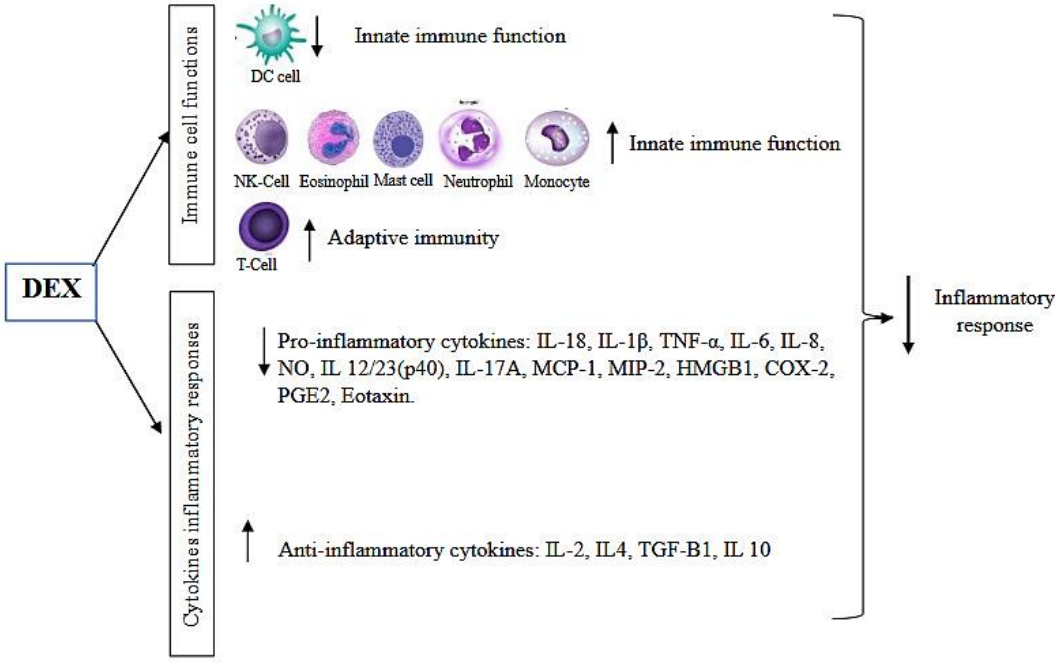

Figure 2. The effect of dexmedetomidine on inflammatory response (21)

Recent studies have demonstrated elevated IL-18 levels in cardiac tissue subjected to myocardial ischemia/reperfusion and sepsis. Specifically, both the non-infarcted and infarcted regions of the left ventricular myocardium exhibit a significant upregulation of pro-IL-18 protein and IL-18 mRNA following an episode of ischemia/reperfusion. According to immunohistochemical analysis, a specific IL-18 signal is present in the smooth muscle and endothelial cells of the heart. Furthermore, the left ventricular ischemic myocardium of patients diagnosed with ischemic dilated cardiomyopathy exhibits a notable upregulation in both mature IL-18 protein expression and IL-18 messenger RNA (mRNA) levels. The primary cellular sources of both IL-18 and its receptor alpha subunit (IL-18Rα) within the ischemic myocardium have been identified as cardiomyocytes, endothelial cells, and macrophages. This observation suggests an upregulation of IL-18 signaling pathways in the context of human heart failure (23).

Elevated IL-18 activity has been identified as a potential indicator of several adverse cardiac events, including inflammation, tissue damage, hypertrophy, functional impairment, and ECM remodeling (9,10). Furthermore, IL-18, following its cleavage by NLRP3, has been shown to activate the STAT3/FOXO3/CXCL-16 signaling pathway, thereby accelerating cardiac injury and inflammatory processes induced by ischemia/reperfusion (12). A study has indicated that IL-18 primarily induces cardiac inflammation through the upregulation of TNF-α, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), IFN-γ, and IL-1β. Furthermore, IL-18 contributes to the development of cardiac fibrosis, hypertrophy, apoptosis, and contractile dysfunction, alongside a reduction in β-adrenergic receptor responsiveness (23). The inflammasome-mediated activation of IL-18 contributes to pathological cardiac inflammation, characterized by macrophage infiltration and myocardial alterations, through rapid overstimulation of the β-adrenergic receptor (19). Furthermore, it is hypothesized that IL-18-activated lymphocytes induce cytotoxicity in endothelial cells, potentially leading to glycocalyx disruption and adverse outcomes during or immediately following CABG (10). Despite the existence of endogenous inhibitors such as IL-18-binding protein (IL-18-BP) and interleukin-37 (IL-37), pharmacological interventions are often necessary to suppress IL-18 activity (8).

The effect of dexmedetomidine on immune system

Dex, a non-opioid anesthetic agent and a selective α2 adrenergic receptor agonist, exerts beneficial effects in mitigating inflammation and myocardial injury during cardiac surgery. These protective roles are attributed to its anti-inflammatory, anti-apoptotic, antioxidant, and anti-stress properties, as well as its capacity to activate the innate immune system (13-17). The pharmacological mechanism of action of Dex is distinct from commonly employed sedative agents, such as clonidine. Specifically, Dex functions as a full agonist at α2 adrenergic receptors (24). Activation of these receptors within the brain and spinal cord leads to the inhibition of neuronal firing, consequently resulting in hypotension, bradycardia, sedation, and analgesia (25,26). Therefore, Dex is utilized in open-heart surgery to mitigate hemodynamic instability and inflammatory responses. This is achieved through its direct agonistic effect on vascular α2 receptors and indirectly via modulation of sympathetic nerve activity (27). The interplay between the immune and adrenergic systems is a close one. Both innate and adaptive immune cells express adrenergic receptors, enabling their direct responsiveness to the sympathetic nervous system. Postganglionic sympathetic nerve fibers, which predominantly release norepinephrine as their primary neurotransmitter, innervate both primary and secondary lymphoid tissues (28).

Dex is a highly selective agonist of the α2 adrenergic receptor, exhibiting a pronounced affinity for the α2A adrenergic receptor subtype. Its immunomodulatory action is primarily mediated through the activation of α2 receptors on the presynaptic membrane, which subsequently regulates the release of norepinephrine. Furthermore, research has indicated that Dex possesses the capacity to modulate cellular immunity, attenuate inflammatory responses within tissues, and enhance the overall immune function in patients (21). It also manages the CD^4+/CD^8+ ratio and regulates the levels of Th1 by activating T lymphocytes and macrophages through interleukin-2 (IL-2) and interferon alpha (INF-α). Additionally, it influences Th2 by promoting B lymphocytes to produce immunoglobulins through IL-4, IL-6, and IL-10, and it supports Type 17 helper (Th17) T cells by increasing the need for neutrophils at the site of inflammation via interleukin-17 (IL-17A), as well as regulatory T cells (Tregs) in adaptive immunity (21,29). The diverse functions of Dex are depicted in Figure 2, highlighting its anti-inflammatory properties.

Conclusion

In conclusion, Dex exerts immunomodulatory effects by mediating the interplay between the α2 adrenergic receptor and the immune system. This regulation involves both innate and adaptive immune cells, which exhibit direct responsiveness to the sympathetic nervous system. The immunomodulation is achieved through the drug's capacity to modulate norepinephrine release by activating presynaptic α2 receptors. This action subsequently leads to the control of cellular immunity, the attenuation of inflammatory responses within tissues, and an enhancement of patients' immune function following cardiac surgery.

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The latter is mediated by the downregulation of the IL-18 signaling pathways originating from various immune and tissue-resident cells, including macrophages, epithelial cells, T cells, neutrophils, NK-T cells, and B cells.

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Ethical statement

This article is derived from the author's PhD thesis and ethical approved by Golestan University of Medical Sciences, Gorgan, Iran (IR.GOUMS.REC.1403.128).

Conflicts of interest

The authors have no conflict of interest.

Author contributions

BMJH and AE: Conceptualization, clarification of data, and writing the original draft and final version; AJ and AM: Writing and editing. All authors equally contributed to the approval of the final version.

Data availability statement

Data can be provided upon request.

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