Dexmedetomidine May Produce Extra Protective Effects on Sepsis-induced Diaphragm Injury

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Abstract

Objective: The objective was to evaluate the protective effects of dexmedetomidine (DEX), a selective agonist of α2-adrenergic receptor, on sepsis-induced diaphragm injury and the underlying molecular mechanisms.

Data Sources: The data used in this review were mainly from PubMed articles published in English from 1990 to 2015.

Study Selection: Clinical or basic research articles were selected mainly according to their level of relevance to this topic.

Results: Sepsis could induce severe diaphragm dysfunction and exacerbate respiratory weakness. The mechanism of sepsis-induced diaphragm injury includes the increased inflammatory cytokines and excessive oxidative stress and superfluous production of nitric oxide (NO). DEX can reduce inflammatory cytokines, inhibit nuclear factor-kappaB signaling pathways, suppress the activation of caspase-3, furthermore decrease oxidative stress and inhibit NO synthase. On the basis of these mechanisms, DEX may result in a shorter period of mechanical ventilation in septic patients in clinical practice.

Conclusions: Based on this current available evidence, DEX may produce extra protective effects on sepsis-induced diaphragm injury. Further direct evidence and more specific studies are still required to confirm these beneficial effects.

Key words: Dexmedetomidine; Diaphragm; Drug Effects; Sepsis

INTRODUCTION

Sepsis is a systemic inflammatory response to infection, with high morbidity and mortality in a clinical setup.[1] Patients with sepsis are hyper-stressed and often require drugs for sedation and analgesia to reduce anxiety and stress. Severe sepsis is also frequently associated with acute lung injury, which necessitates mechanical ventilation support.[2,3] Hence, a sedative agent is required in patients with sepsis.

Dexmedetomidine (DEX), a selective agonist of α2-adrenergic receptor, is widely used in intensive care units due to its sedative and analgesic effects. Based on available literature search, The Canadian Agency for Drugs and Technologies in Health stated that DEX was associated with a shorter period of mechanical ventilation and lower intensive care unit stay when compared with traditional sedative agents such as midazolam and propofol.[4] The latest meta-analysis done in 2014 covering 1624 participants found that DEX also could reduce breathing support time by approximately one-fifth and consequently the length of stay time in intensive care units by one-seventh in patients requiring long-term sedation (more than 24 h) under mechanical ventilation.[5] This can be explained by the anti-inflammatory, organ-protective, and anti-sympathetic properties of DEX.[5,6]

In septic animals, DEX was effective in suppressing the inflammatory response and thus decreasing mortality rates.[7-11] Similarly, in a clinical setup, DEX infusion decreased inflammatory cytokine production significantly compared with midazolam[12] and propofol[13] in septic patients. Considering these anti-inflammatory effects, DEX can improve 28-day survival rates compared with lorazepam in patients with sepsis.[6]

Sepsis can induce severe diaphragm dysfunction[14,15] and exacerbate respiratory weakness.[16] A recent study indicates that during sepsis, diaphragm is much more affected as compared with limb muscle.[17] Sepsis involves a network of over-expressed inflammatory cytokines which have been proved to be associated with diaphragm dysfunction.[18,19] Due to its significant anti-inflammatory and organ-protective properties, we think DEX may produce extra protective effects on sepsis-induced diaphragm injury when used in septic patients for sedation

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and analgesia. In this review, we summarize the potential molecular mechanisms.

MOLECULAR MECHANISMS OF SEPSIS-INDUCED DIAPHRAGM INJURY

In animals, sepsis can induce an increase in plasma inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[20,21] Not only in plasma, sepsis also can increase inflammatory cytokines in muscles,[22,23] and muscle cells apparently constitute an important source of cytokines during sepsis.[23] Similarly, in human volunteers, skeletal muscle is capable of producing essential inflammatory mediators after endotoxin stimulation.[24] Hence, sepsis can induce comprehensive inflammatory response.

In dogs, TNF-α infusion is associated with a significant decline in isotonic and quasi-isometric diaphragm contraction.[25] In rats, after endotoxin injection, gene expression and production of TNF-α are elevated in the diaphragm tissue, and anti-TNF-α antibody preinjection can prevent the deterioration of the diaphragm muscle contractile properties.[18] Hence, TNF-α is an important mediator of sepsis-related impairment in diaphragm contractility. Possible mechanisms include: Activating caspase-8 and -3 pathway,[26] increasing oxidant activity in muscle fibers,[27,28] and activating nuclear factor-kappaB (NF-κB) signaling pathways.[29] Moreover, plasma from patients with septic shock can induce *in vitro* loss of myosin in skeletal myotubes, which is significantly associated with elevated plasma levels of IL-6 in septic shock patients.[19] With elevated serum IL-6 concentration, the muscle of IL-6 transgenic mice suffers from atrophy, which can be completely blocked by treatment with the anti-mouse IL-6 receptor antibody.[30] Lipopolysaccharide (LPS) induced sarcolemmal damage in diaphragm myofibers is accompanied by a significant increase in IL-1beta expression in the tissues.[31] IL-1alpha and -1beta can reduce myofibrillar protein in differentiated myotubes,[32] and IL-1 receptor antagonist can maintain the synthesis of both myofibrillar and sarcoplasmic proteins during sepsis.[33] One possible mechanism of IL-6 and -1 in inducing diaphragmatic contractile dysfunction is to stimulate NF-κB signaling and increase expression of atrogin1/muscle atrophy F-box and muscle RING-finger protein-1.[19,32] Hence, sepsis induces increase in inflammatory cytokines such as TNF-α, IL-6 and -1, which can lead to diaphragmatic force loss and atrophy.

Besides, sepsis can enhance oxidative stress in the skeletal muscle,[34,35] with diaphragm being no exception.[36] Sepsis-induced oxidative stress in the diaphragm can induce protein carbonyl formation,[37] impair mitochondrial respiratory functioning,[38,39] thus leading to diaphragmatic contractile dysfunction. Sepsis also can increase the activity of inducible nitric oxide synthase (iNOS),[40,41] which increases the amount of NO in diaphragm. NO can inhibit antioxidant enzyme activity[42] and increase oxidative stress.[43] NO also can produce excessive peroxynitrite and stimulate protein nitration formation in the mitochondrial matrix,[44,45] resulting into diaphragmatic mitochondrial dysfunction and contractile failure. Hence, sepsis induces excessive oxidative stress and superfluous production of NO which leads to diaphragmatic contractile dysfunction.

MOLECULAR MECHANISMS OF DEXMEDETOMIDINE IN DECREASING SEPSIS-INDUCED DIAPHRAGM INJURY

Dexmedetomidine can inhibit the increase of serum levels of TNF-α, IL-6 in endotoxemic rats[10,11] and in cecal ligation and puncture (CLP)-induced septic rats[7] and mice.[8] DEX also can attenuate the LPS-induced increase of inflammatory factor IL-1beta[9] and -8.[46] This suppressing effect of DEX on inflammatory mediators during sepsis is proved to be dose-dependent,[11] and the clinical using dose of DEX is proved to have the suppressing effect of LPS-induced inflammatory mediator production.[46] *In vitro*, DEX takes effects via α2-adrenergic receptors.[46] *In vivo*, it functions through its sympatholytic effect that leads to the activation of the vagus nerve, which then stimulates cholinergic anti-inflammatory pathway.[9] Hence, DEX may attenuate diaphragm atrophy and weakness in sepsis due to the inhibition of inflammatory cytokines by its anti-inflammatory effects.

In septic rats, DEX can significantly suppress CLP-induced NF-κB activation in lung tissue.[7] Moreover, after LPS stimulation, DEX also has an inhibitory effect on NF-κB activation in human whole blood.[46] Furthermore, in LPS-activated macrophages, DEX inhibits the translocation of NF-κB from the cytoplasm to the nucleus at clinically relevant dosages via α2-adrenergic receptors.[47] As inflammatory mediators can induce diaphragm atrophy by activating NF-κB signaling pathways,[19,29,32] DEX may produce protective effects in diaphragm muscle by inhibiting them.

In primary diaphragm muscle cell cultures, pharmacologic blockade of the NF-κB pathway and dominant-negative molecular inhibition of IκB kinase-beta strongly suppresses LPS-induced pro-inflammatory gene expression.[48] Moreover, in muscle-specific IκB-alpha super-repressor mice subjected to endotoxemia, the increase of pro-inflammatory cytokines in the diaphragm can be prevented.[49] These two experiments indicate that NF-κB signaling within skeletal muscle fibers is a key pathway leading to diaphragmatic weakness during sepsis, most likely via effects on multiple inflammatory mediators.[48,49] As inflammatory mediators can activate NF-κB signaling pathways,[19,29,32] inflammatory mediators and NF-κB can stimulate each other reciprocally. DEX may be able to break this vicious cycle by both suppressing inflammatory mediators and NF-κB signaling pathways.
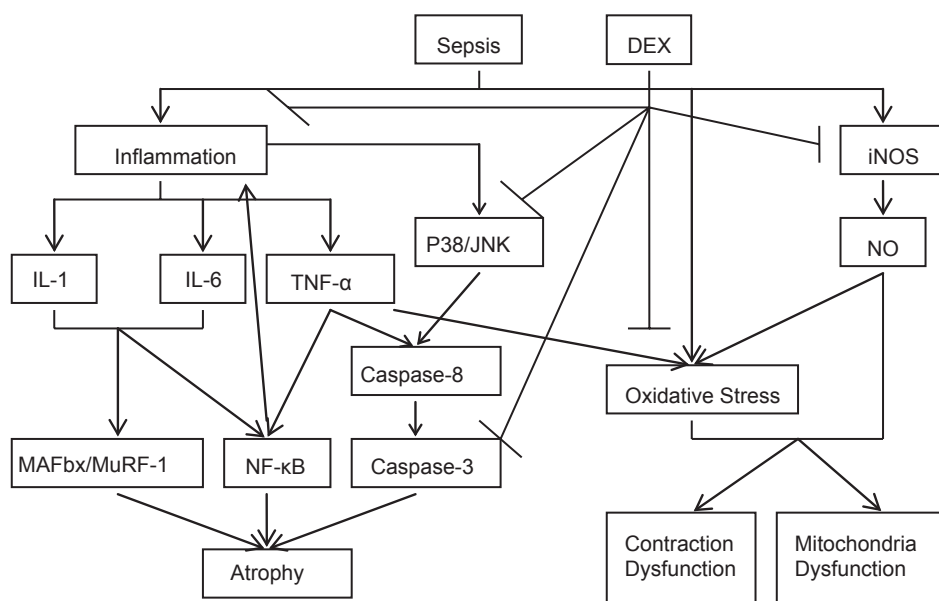
Figure 1: DEX: Dexmedetomidine; IL-1: Interleukin-1; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; JNK: Jun N-terminal kinase; MAFbx: Muscle atrophy F-box; MuRF-1: Muscle RING-finger protein-1; iNOS: Inducible nitric oxide synthase; NO: Nitric oxide; ↓activation; ⊥inhibition.

Caspase-3 can break down actomyosin complexes, yielding proteins that are degraded by the ATP-ubiquitin-proteasome system. So in catabolic conditions, activation of caspase-3 is an initial step triggering accelerated muscle proteolysis.[50] Endotoxin administration can elicit significant diaphragm caspase-3 activation and caspase-mediated diaphragmatic weakness.[51] DEX can inhibit caspase-3 expression, attenuating isoflurane-induced injury in developing brain[52] or ischemia/reperfusion injury in the retina.[53] Thus, by inhibiting the activation of caspase-3, DEX may produce protective effects in diaphragm muscle during sepsis. In addition, both endotoxin and inflammatory cytokines can first activate p38[54] and Jun N-terminal kinase (JNK)[55] pathway, then triggering caspase-8 and -3 pathway[26] to induce diaphragm weakness. Luckily, DEX pretreatment can inhibit isoflurane-induced neuroapoptosis by inhibiting p38 and JNK pathways.[56] So by suppressing the upstream p38 and JNK pathways, DEX may further protect diaphragm muscle against sepsis-induced proteolysis.

It is proved that both antioxidant and NOS inhibitor can ameliorate diaphragmatic dysfunction.[57,58] Moreover, in acid-induced acute lung injury, preemptive use of DEX produces important protective effects on the liver against oxidative stress.[59] In pneumoperitoneum-related ischemia-reperfusion injury, DEX is proved to be effective in decreasing systematic[60] and local[61] oxidative stress. DEX can also markedly reduce the oxidative stress in skeletal muscle due to ischemia-reperfusion injury and exhibit more potent antioxidant activity than vitamin E.[62] Furthermore, short-term use of DEX can reduce iNOS in LPS-induced acute lung injury compared to thiopental sodium.[63] DEX can attenuate LPS-induced iNOS and NO accumulation in primary microglia[64,65] by inhibiting extracellular signal-regulated kinase activation.[65] Hence, DEX may preserve muscular force in sepsis by inhibiting excessive oxidative stress and the superfluous production of NO.

In clinical practice, septic patients treated with DEX have shorter time on the ventilator as compared with those treated with lorazepam, a benzodiazepine and this beneficial effect of DEX is more pronounced in septic patients than in nonseptic patients.[6] This outcome may be partly the result of DEX-induced reduction in pulmonary inflammatory mediators and lung tissue damage.[7] However, based on the molecular mechanisms discussed above, this outcome may be also the result of DEX-induced extra protective effects on sepsis-induced diaphragm injury.

In conclusion, when used in patients with sepsis for sedation and analgesia, DEX may produce protective effects on diaphragm against sepsis-induced injury. The mechanisms include reducing inflammatory cytokines, inhibiting NF-κB signaling pathways, suppressing the activation of caspase-3, decreasing oxidative stress, and inhibiting iNOS [Figure 1]. As most of the mechanisms come from the studies of the protective effects of DEX on other organs in sepsis or other organ injury models, further direct evidence is still needed to confirm these beneficial effects.

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