

# The role of dexmedetomidine in immune tissue and inflammatory diseases: a narrative review

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**Abstract. – OBJECTIVE:** Adrenergic receptors belong to the G protein-coupled receptor family and are one of the important targets of modern drug therapy. Dexmedetomidine (DEX) is a highly selective agonist of alpha2 receptor, a member of the adrenergic receptor family, which are widely found in immune tissues and which mediate the biological behaviour of the inflammatory immune system. This review mainly summarizes the role of DEX in immune tissue and inflammation-related diseases, to provide a theoretical basis for clinical treatment.

**MATERIALS AND METHODS:** We searched the PUBMED, EMBASE, and Cochrane libraries separately to obtain published literature on DEX related to immune tissue and inflammatory diseases. The mesh (dexmedetomidine, microglia, astrocytes, spleen, marrow, lymph nodes) and their corresponding keywords used for the searches, and no time limit for retrieval. The latest search was conducted on July 1, 2022.

**RESULTS:** By reading a lot of relevant literature, we found that DEX reduces the inflammatory response of brain tissue by interfering with microglia and astrocytes. DEX can regulate the expression of CD40 and CD86 markers on the surface of splenocytes and reduce the secretion of inflammatory cytokines by splenocytes. In addition, we found that DEX reduced inflammation-related diseases such as neuroinflammation, myocarditis, liver cirrhosis, osteoarthritis, upper respiratory tract infection, pancreatitis, spinal tuberculosis, pulpitis, colon inflammation and rheumatoid arthritis, and improved prognosis.

**CONCLUSIONS:** DEX has anti-inflammatory and improved prognosis in many inflammatory related diseases and is expected to become a targeted drug for the treatment of inflammatory diseases.

*Key Words:*

Dexmedetomidine, Immune tissues, Inflammatory diseases, Microglia, Astrocytes.

## Introduction

Adrenergic system refers to adrenergic receptor, epinephrine, norepinephrine, enzymes and messengers of norepinephrine or drug binding pathways associated with signal transduction<sup>1</sup>. Two adrenergic neurotransmitters, epinephrine and norepinephrine (NA), act on  $\alpha$  adrenergic receptor ( $\alpha$ -AR) and  $\beta$  Adrenergic receptor ( $\beta$ -AR) and regulates a variety of biological functions<sup>2</sup>. Adrenergic receptors belong to G protein coupled receptor family and are a key target in modern drug therapy<sup>1</sup>.

The  $\alpha_2$  receptor is coupled with multiple signaling pathways, mainly activating the G-protein-gated inwardly rectifying K<sup>+</sup> Channels (GIRK), mitogen-activated protein kinase (MAPK) and phospholipase D and inhibiting the Ca<sup>2+</sup> pathway and adenylate cyclase<sup>3</sup>. The  $\alpha_2A$  receptors function as presynaptic feedback, inhibition of noradrenaline release, hypotension, analgesia, sedation and inhibition of epileptic seizures. The  $\alpha_2B$  receptors play a role in hypertension and placental angiogenesis. The subtype of  $\alpha_2C$  is mainly associated with dopamine neurotransmitters, which can induce a decrease in body temperature and a series of behavioral responses.

Dexmedetomidine (DEX) is a highly selective agonist of  $\alpha_2$  receptor, belonging to the adrenergic system, of which mainly acts on  $\alpha_2A$ -AR and  $\alpha_2C$ -AR. It is common knowledge that  $\alpha_2A$ -AR and  $\alpha_2C$ -AR are widely distributed in the brain and spleen, which are critical immune tissues<sup>4</sup>. Then, the specific role and mechanism of DEX on immune tissue and related diseases will be the focus of researchers.

In this review, we summarized the role of DEX in immune tissues (brain, spleen, marrow and

lymph nodes) and immune diseases in order to provide a theoretical basis for clinical treatment.

## Materials and Methods

### Searching Strategy

Two researchers searched PUBMED, EM-BASE, and Cochrane library independently. The mesh (dexmedetomidine, microglia, astrocytes, spleen, marrow, lymph nodes) and their corresponding keywords used for the searches, and the article publishing time have not been set. The latest search was conducted on July 1, 2022. Furthermore, investigators scanned references of these articles to prevent missing articles. The flow chart is presented in Figure 1.

### Inclusion and Exclusion Criteria

Published English articles on DEX and immune tissues (microglia, astrocytes, spleen, bone marrow and lymph nodes) or inflammation were included in our review. The study would be excluded if it is: (1) a duplicate article; (2) there was a clear error in the data; (3) conference reports, letters, comments or economic analysis; and (4) we had not obtained the full text of the study by various methods.

### The effect of DEX on Immune Tissues

#### Distribution of $\alpha_2$ -AR in human tissues

Research report,  $\alpha_2$ A-AR and  $\alpha_2$ C-AR is widely distributed in brain and spleen tissues<sup>4</sup>, as shown in Table I. Coincidentally, DEX is highly selective  $\alpha_2$ -AR agonist, which mainly acts on  $\alpha_2$ A-AR and  $\alpha_2$ C-AR.

### Brain

The brain is the central core of neuroendocrine immune network, regulating all immune activity in the center. The immune response in the central nervous system is mediated by resident microglia and astrocytes. Microglia are actually macrophages in the central nervous system. Though astrocytes have been regarded as non-invasive supporting cells, in recent years, novel functions of astrocytes have been discovered.

### Microglia

Microglia are the resident macrophages and the immune cells of the central nervous system, which play an important part in neuroinflammation. When inflammation, infection, trauma or other neurological diseases occur in the brain, microglia are rapidly activated and obtain phagocytic function. Over activated microglia can produce excessive pro-inflammatory mediators, such as: NO, prostaglandin E2 (PGE2), TNF- $\alpha$  and interleukin-1 $\beta$  (IL-1 $\beta$ )<sup>4</sup>.

It is believed that DEX pretreatment can reduce the expression of pro-inflammatory mediators in microglia, such as: NO, iNOS, PGE2, TNF- $\alpha$ , COX II, IL-1 $\beta$ , IL-6 and IL-18, increase the level of anti-inflammatory mediator IL-10, so as to inhibit the inflammatory reaction<sup>5-9</sup>. It is believed that when the DEX concentration is greater than the clinical concentration, it affects the expression of pro-inflammatory mediators. Meng et al<sup>7</sup> believed that DEX can inhibit the expression of inflammatory mediators by upregulating the expression of sirtuin-1 (SIRT1) in microglia and inhibiting the expression and glycolysis of hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ). Zhang et al<sup>8</sup> thought that DEX could attenuate endotoxin

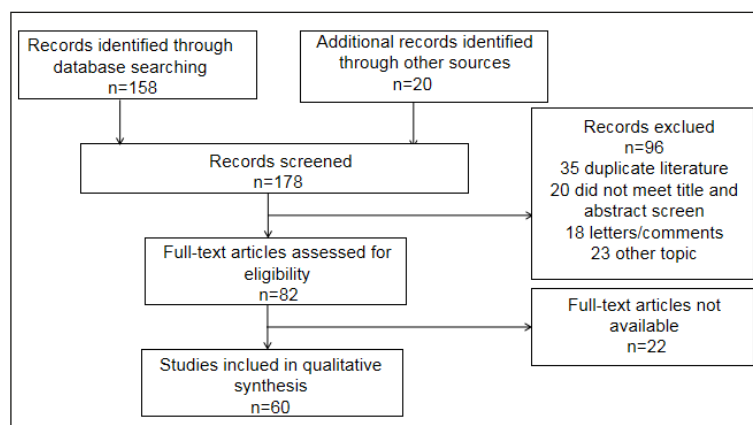


Figure 1. Flow chart for articles selection.

**Table I.** Distribution of  $\alpha_2$ -AR in human body.

Types of -AR	Human tissue distribution
$\alpha_2A$	Brain > spleen > kidney > aorta = lung = skeletal muscle > heart = liver
$\alpha_2C$	Brain = kidney (also reported in spleen, aorta, heart, liver, lung, skeletal muscle)

induced down-regulation of CD200R expression in microglia through Dok1/Ras/ERK/PI3K/NF- $\kappa$ B pathway. Li et al<sup>9</sup> suggested that DEX could inhibit the inflammatory response of microglia, stimulated by lipopolysaccharide (LPS) and ATP, through the c-Fos/NLRP3/caspase-1 cascade. Zhou et al<sup>10</sup> believed that DEX could reduce the release of TLR4 and NF- $\kappa$ B in a dose-dependent manner, playing an anti-inflammatory role.

Similar to macrophages, activated microglia have two phenotypes: classic activation (M1) phenotype and alternate activation (M2) phenotype. Activation of M1 phenotype promotes the expression of pro-inflammatory mediators, such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, iNOS and NO, and promote the transformation of T cells to Th1 and Th17. As for M2, it can improve the expression of anti-inflammatory mediators, such as IL-10 and M2 marker genes (cd206, Arg-1, fizz-1, Mrc1), thereby reducing injury and inflammation<sup>10-14</sup>. Many studies<sup>15-23</sup> have shown that DEX can play an anti-inflammatory role by inhibiting the expression of pro-inflammatory genes, upregulating the expression of anti-inflammatory mediators and M2 type marker genes and promoting the M2 phenotype polarization of microglia.

The mechanism of microglia polarization involves a variety of molecules and signaling pathways. It has been noted that DEX may regulate microglia M1/M2 polarization through Akt signaling pathway<sup>16-19</sup>. Experiments found that DEX could increase the polarization of M2 by inhibiting ERK1/2 phosphorylation, namely ERK signaling pathway<sup>15,20,21</sup>. Animal experiments discovered that DEX may inhibit the expression of IL-17A through cholinergic anti-inflammatory pathway, thus promoting the polarization of M2<sup>22</sup>. *In vitro* and rat models, DEX can upregulate the expression of programmed cell death protein-1 (PD-1) in microglia, advance the activation of AMPK signaling pathway in microglia, and then promote the microglia polarization to M2 type<sup>23</sup>.

In conclusion, regulation of DEX on M1/M2 polarization of microglia may be a vital mechanism of its anti-inflammatory effect. The effects of DEX on these signaling pathways may depend on cell and tissue types and inflammatory environment, which

should be further studied. The above findings are based on animal cell trials, have not been confirmed in clinical studies, and further research is needed.

### Astrocytes

Astrocytes are one of many kinds of glial cells in the central nervous system. They are widely involved in the differentiation of nerve and the regulation of immune response. They play an important role in the immune regulation of the central nervous system (CNS)<sup>24-27</sup>.

DEX attenuates sepsis-associated inflammation and encephalopathy through central  $\alpha_2A$  adrenergic receptors, the mechanism of which may be mediated by  $\alpha_2A$  adrenergic receptors in astrocytes<sup>28,29</sup>. An interesting finding was that astrocytes expressed  $\alpha_2A$  adrenaline receptors, while microglia did not, so a decrease in microglia did not eliminate the protective effect of DEX on LPS-induced sepsis brain damage<sup>28</sup>. DEX attenuates LPS induced MCP-1 expression, a major pro-inflammatory factor, in primary astrocytes, thereby alleviating neuroinflammation<sup>30</sup>. DEX can alleviate the amount of Caspase-1 immune response and the release of pro-inflammatory cytokines IL-1 $\beta$  and IL-18 promoted by LPS treated rat astrocytes *in vitro* and *in vivo* models, thus easing neuronal damage<sup>31</sup>. Moderate and high concentrations (1  $\mu$ M and 10  $\mu$ M) of DEX pretreatment could inhibit the inflammatory response of astrocytes induced by LPS, and downregulate the expression of pro-inflammatory factors iNOS, TNF- $\alpha$  and IL-1 $\beta$ <sup>32</sup>. DEX can inhibit IL-6 synthesis induced by IL-1 $\beta$  in astrocytes by  $\alpha_2$ -AR, but not on adenosylacylase-cAMP pathway<sup>29</sup>. DEX inhibits TNF- $\alpha$  and IL-6 in LPS stimulated astrocytes by inhibiting c-Jun N-terminal kinase rather than p38 MAPK signaling pathway<sup>29</sup>. IL-6 may be an effective therapeutic target for central nervous system diseases, of which it plays a critical role in neuroinflammation accompanied by encephalopathy. Astrocytes are thought to be the primary source of IL-6 in the CNS, and DEX may affect the central nervous immune system by regulating the production of IL-6 on astrocytes<sup>5,29,33</sup>. Therefore, DEX is expected to become a targeted drug for the treatment of central nervous system diseases and neuroinflammation. The above con-

clusions are mainly obtained through animal cell experiments.

DEX can protect astrocytes, regulate their morphology and inhibit their apoptosis. DEX can inhibit the formation of camp dependent and independent processes by acting on  $\alpha_2$ -AR of astrocytes, thus inhibiting the formation of astrocytes and regulating their morphology in animal cell models<sup>34</sup>. DEX protects astrocytes against apoptosis by inhibiting JAK2/STAT3 signaling pathway and downregulating the expression of histone demethylase JMJD3 *in vitro*<sup>35</sup>. DEX can inhibit histone release, significantly reduce apoptosis and necrosis, protect glial cells and neurons, then protect brain function and ultimately improving the prognosis of sepsis *in vitro* and *in vivo* models<sup>31</sup>.

Astrocytes have the function of antigen presentation and participate in the activation of Th1 cells<sup>36,37</sup>. It has also been confirmed<sup>38</sup> that inflammation triggers a positive feedback circuit between astrocytes and Th1 cells through IFN- $\gamma$ , which promotes the occurrence of inflammatory pain. However, astrocytes inhibitors cannot be used in clinical practice because of severe neurotoxicity. As for DEX, it can act not only on Th1 cells but also on astrocytes and affect the secretion of IFN- $\gamma$ , which may become a new target drug in inflammatory pain.

In conclusion, DEX can protect astrocytes, act on  $\alpha_2$ -AR on astrocytes to play an anti-inflam-

matory role, mitigate sepsis related inflammation and encephalopathy, and is expected to become a targeted drug for the treatment of central nervous system diseases, neuroinflammation and inflammatory pain. However, systematic clinical results validation is still lacking, and further research is needed.

### Spleen

Similar in structure to lymph nodes, the spleen is an important component of the mononuclear phagocytosis system. In addition, the spleen produces antibodies to clear bacteria or senescent blood cells. At least half of the mononuclear cells in spleen can differentiate into dendritic cells and macrophages, which are major immune cells. The study<sup>39</sup> has found that DEX can regulate the expression of CD40 and CD86 markers on the surface of splenocytes, narrow the secretion of inflammatory cytokines IL-1  $\beta$ , IL-6, IL-8 and TNF- $\alpha$  in splenocytes without affecting their activity, and DEX at a higher concentration (100  $\mu\text{g}/\text{ml}$ ) has a better effect in reducing inflammation than that at a lower concentration (30  $\mu\text{g}/\text{ml}$ ) in mice. In the study of the analgesic effect of DEX on spleen in mice, Jang et al<sup>40</sup> confirmed that DEX can reduce the activation of NK cells in formalin pain model but has no effect on the proliferation of splenic lymphocytes and the production of cytokines. At present, research of DEX on spleen

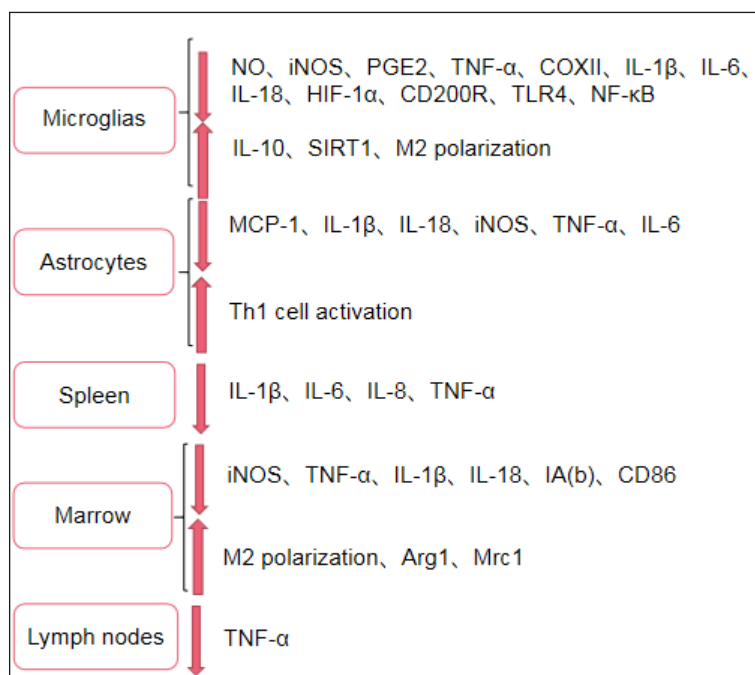


Figure 2. The effect of DEX on cells and immune organs.

cells is less, but the  $\alpha$ -AR are mostly distributed in spleen tissue, which is worth further research.

### *Marrow*

The blood components in the human body are in a constant metabolism, the old cells are removed, and new cells are generated. An important function of bone marrow is to produce stem cells that can differentiate and regenerate into various blood cells, such as red blood cells, white blood cells, platelets, etc. Therefore, bone marrow plays an important role in maintaining human life and immunity.

*In vitro*, DEX can prevent HMGB1-induced cell death of bone marrow-derived macrophages (BMDMs), inhibit the production of TNF- $\alpha$ , IL-1 $\beta$  and IL-18, and inhibit the phosphorylation of ERK1/2 and P38<sup>41</sup>. Furthermore, DEX inhibits the activation of caspase-1 and reduces pyroptosis of BMDMs<sup>41</sup>. Using a mouse bone marrow-derived dendritic DC2.4 cell line, DEX promoted inflammatory cytokine production at high clinical concentrations (10, 1, and 0.1  $\mu$ M), but not at the lowest clinical concentration (0.001  $\mu$ M), which is associated with NF- $\kappa$ B and c-Jun N-terminal kinase (JNK)-MAPK signaling<sup>42</sup>. In mouse bone marrow-derived dendritic cells (DCs), DEX significantly delayed the intracellular proteolytic degradation of ovalbumin, but it had no impact on phagocytosis, decreased the expression of surface molecules IA(b) and CD86, and inhibited recognition function<sup>43</sup>. In addition, DEX significantly inhibited DCs migration *in vitro*, which may be related to inhibition of type IV collagenase/gelatinase activity<sup>43</sup>. Pretreatment with DEX but not propofol enhanced the efficacy of human bone marrow mesenchymal stem cells (hBM-MSCs) in hepatic ischemia-reperfusion injury (HIRI)<sup>44</sup>. It is worth noting that the above studies<sup>41-44</sup> mainly focus on the animal or cell experiments, and the observation of the effect of DEX on human bone marrow has not been reported.

### *Lymph Nodes*

Lymph node is a unique organ of mammals and an important immune organ of the human body. In an experimental model of sodium iodoacetate-induced knee osteoarthritis in rats, DEX reduced TNF- $\alpha$  levels in popliteal lymph nodes for 28 days, significantly reduced body weight distribution defects in animals, and increased pain thresholds<sup>45</sup>. At present, there are few research findings on the effect of DEX on lymph nodes, which may become a future research area to further explore the role of DEX in immune tissue.

### *The Role and Related Mechanisms of DEX in Inflammatory Immune Diseases*

DEX has been proved to inhibit the inflammatory response in a variety of diseases, and exert an immunomodulatory role in inflammatory diseases, and the relevant mechanisms are shown in Table II.

Based on the literature of basic studies<sup>5,46-48</sup>, we found that DEX exhibits a potent anti-inflammatory effect. DEX may play an anti-neuroinflammatory role by upregulating mir-340, inhibiting the activation of NLRP3 inflammasome and the expression of Caspase-1, and directly inhibiting the activation of microglia. In animal models, DEX can promote the viability of cardiomyocytes, inhibit their apoptosis, and reduce the inflammatory reaction<sup>49</sup>. DEX can ameliorate the osteoarthritis pain score and cartilage tissue damage by inhibiting the activation of NF- $\kappa$ B and NLRP3 inflammasome<sup>50</sup>. DEX can stimulate central  $\alpha_2$ -AR, significantly decrease the levels of serum amylase, lipase, IL-1 $\beta$ , IL-6, TNF- $\alpha$ , myeloperoxidase (MPO) and pro-inflammatory HMGB1<sup>51</sup>. DEX reduces the activation of NLRP3 inflammasome and upregulates the expression of the norepinephrine transporter (net) to alleviate the systemic inflammatory reaction caused by pancreatitis and local pancreatic pathological injury<sup>52</sup>. In addition, Zhang et al<sup>53</sup> found that in a mice model of LPS-induced acute lung injury, DEX was effective in reducing the level of pro-inflammatory factor in sepsis mice, meanwhile increasing the level of anti-inflammatory factor, and it can play a protective role whether DEX is administered before or after surgery. In the colitis animal model, DEX increased the level of IL-4 and IL-10, reduced the secretion of IL-23, promoted the anti-inflammatory response of Th2 pathway, reduced the inflammatory response induced by Th17 pathway, lowered the specific inflammatory immune response, thereby exerting a protective effect<sup>54</sup>. Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammatory synovitis. DEX has a good therapeutic effect on RA by reducing the expression of nlrp5, reducing the levels of IL-1  $\beta$ , IL-6, MMP-3 and MMP-9, inhibiting cell invasion and migration<sup>55</sup>.

Based on clinical studies<sup>56-60</sup>, we also found that DEX has a potential therapeutic effect on many inflammatory diseases. DEX for patients with cirrhosis improves hemodynamic stability, reduces stress response, and reduces levels of inflammation<sup>56</sup>. In children with recent upper respiratory tract infection, intranasal DEX pretreatment significantly reduced the incidence of

**Table II.** Relevant mechanism of DEX in the treatment of inflammatory diseases.

Disease	Related mechanism	Type of Study
Neuroinflammation	up regulating mir-340 inhibiting the activation of NLRP3 and the expression of Caspase-1 inhibiting the activation of microglia	basic research
Myocardial inflammation	promoting the viability of cardiomyocytes inhibiting cardiomyocyte apoptosis	basic research
Osteoarthritis	inhibiting the activation of NF- $\kappa$ B and NLRP3	basic research
Pancreatitis	stimulating central $\alpha$ 2-AR, reducing IL-1 $\beta$ , IL-6, TNF- $\alpha$ , myeloperoxidase, HMGB1 and the activation of NLRP3	basic research
Colitis	increasing the level of IL-4 and IL-10 reducing the secretion of IL-23 promoting the response of Th2 pathway reducing the inflammatory response induced by Th17 pathway	basic research
Rheumatoid arthritis	reducing the expression of nlr5, IL-1 $\beta$ , IL-6, MMP-3 and MMP-9	basic research
Sepsis lung damage	inhibiting the release of inflammatory factors, increasing the anti-inflammatory factors, down-regulating the expression of MMP9, JAK1, STAT3 in lung tissue	basic research
Liver cirrhosis	reducing stress response and TNF- $\alpha$	clinical research
Upper respiratory tract infection	-----	clinical research
Spinal tuberculosis	reducing the serum TNF- $\alpha$ , IL-6	clinical research
Dental pulp Inflammation	regulating TRPV1 channel	clinical research
HIPEC after surgery	reducing the serum TNF- $\alpha$	clinical research

perioperative respiratory adverse events<sup>57</sup>. In patients with spinal tuberculosis, the serum TNF- $\alpha$ , IL-6 concentrations and the incidence of postoperative pulmonary complications in DEX group were significantly lower than those in the control group at 1 h, 6 h and 1 d after operation, indicating that DEX has significant anti-inflammatory effect and reduces postoperative pulmonary infection<sup>58</sup>. In clinical trials, DEX can induce human dental pulp cells to produce anti-inflammatory activity by regulating TRPV1 channel, which can be utilized as a potential target drug for intervening human dental pulp inflammation<sup>59</sup>. DEX combined with dezocine in patients undergoing hyperthermic intraperitoneal chemotherapy (HIPEC) after

intestinal surgery effectively reduces the level of inflammatory response and myocardial injury-related factors 12 hours after surgery, thus playing a cardioprotective effect<sup>60</sup>.

Based on the above content, the effect of DEX on inflammatory and immune-related diseases is briefly summarized. DEX inhibits NLRP3, HMGB1, IL-1 $\beta$ , IL-6, IL-23, TNF- $\alpha$ , MMP-3 and MMP-9, stimulates central  $\alpha$ <sub>2</sub> receptors, and promotes IL-4 and IL-10 expression, exerts immunomodulatory and anti-inflammatory effects. However, the role of DEX in inflammatory diseases is mostly about animal experiments, and it is necessary to further explore its therapeutic effect in future clinical studies.

## Conclusions

This paper innovatively summarizes the role of DEX in brain microglia, astrocytes, spleen, bone marrow, and lymph nodes, rather than innate immune cells (NK cells, DC cells, etc.) and acquired immune cells (B cells, T cells) (Figure 2).

The effects of DEX on immune tissue are summarized below. DEX pretreatment can reduce the expression of pro-inflammatory mediators in microglia. DEX can promote the M2 phenotype polarization of microglia by promoting the expression of the M2 marker gene, so as to play an anti-inflammatory role. DEX has anti-inflammatory effects on LPS-stimulated astrocytes. DEX protects astrocytes, regulates their morphology and inhibits their apoptosis. Therefore, DEX is expected to become a targeted drug for the treatment of central nervous system diseases, neuroinflammation and inflammatory pain. DEX can regulate the expression of CD40 and CD86 markers on the surface of splenocytes, decrease the secretion of inflammatory cytokines IL-1  $\beta$ , IL-6, IL-8 and TNF- $\alpha$  in splenocytes without affecting their activity. Unfortunately, there are comparatively few studies on DEX in marrow and lymph nodes.

Additionally, we summarize the role of DEX in inflammation-related diseases, and find that DEX can inhibit neuroinflammation, myocarditis, inflammatory bowel disease, liver cirrhosis, osteoarthritis, upper respiratory tract infection, pancreatitis, spinal tuberculosis, pulpitis, colitis and rheumatoid arthritis, and improve the prognosis. This provides the basis for the clinical application of DEX.

The disadvantage of this paper is that most of the experiments are based on animal cells, and there are few human experiments involved, so the reliability of the conclusions of this review is debatable, and of course, further clinical studies in the future to confirm the role of DEX in related inflammatory diseases are necessary.

All in all, we summarized the effects of DEX on immune tissues and inflammatory diseases, which provide a theoretical basis for the application of DEX in immune-inflammatory related diseases.

### Conflict of Interest

The authors declare that they have no competing interests.

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### Authors' Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

### Ethics Committee Approval

Not applicable.

### Informed Consent

Not applicable.

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