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REVIEW ARTICLE

Pandemic aspect of dexamethasone: Molecular mechanisms and clinical application

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Abstract: The rapid spread of coronavirus disease (COVID-19) in many countries has caused inconvenience in conducting daily life activities, and even deaths. Dexamethasone is a corticosteroid applied in clinical medicine since 1957, especially in immune therapy fields. Herein, we present the characteristics of Dexamethasone, from molecular mechanisms such as genomic and nongenomic pathways by cellular signal regulations, to clinical applications in various phases of the disease. During COVID-19 pandemic, Dexamethasone given to patients who required oxygen or ventilation therapy showed improved life efficacy.
Keywords: COVID-19; Dexamethasone; Molecular mechanisms

1. INTRODUCTION

Currently, several fields of medicine are involved in COVID-19 treatment. Mainly validated approaches demonstrated a potent efficacy against coronavirus, including Remdesiviir (an antiviral drug) and developed vaccines.[1] Dexamethasone applied for COVID-19 patients has shown to be effective in combating the virus.[2] We would like to concentrate here on the origin of Dexamethasone in clinical therapy, on the basis of its molecular signal mechanisms to mandatory treatment.

1.1. Steroids

Steroids had been applied in many medical research and clinic therapy for years.[3] Natural steroids are hydrophobic compounds found in fungi, plants, animals, and humans.[4] Steroids function as signal molecules composed of a 4-ring core structure (A, B, C, and D) and 17 carbon atoms distributed within the cellular membrane. They are originally formed from sterol lipid (cholesterol) synthesized with acetyl-coenzyme A via HMG-CoA reductase pathway.[5] According to the modification in their ring structures, steroids can be grouped into androgen, estrogen, or anti-inflammatory glucocorticoids (GCs).

1.2. Glucocorticoid

GCs belong to the major corticosteroid hormones produced in mammalian adrenal cortex. GCs play diverse functions during our physiological processes, including immune and stress response, regulation of blood electrolyte, and behavior control.[6]

In response to stress, our hypothalamus secrets a corticotrophin-releasing hormone to stimulate corticotrophin at the hypophysis gland, where GCs are produced and streamed into blood.[7] Natural and synthetic steroid hormone such as Dexamethasone affect lipid, protein, and carbohydrate metabolism by exerting its anti-inflammatory, immunosuppressive, bone mineralization, vasoconstrictive effects, and its impact on the central nervous system.[8]

1.3. GC receptor

GCs regulate many essential physiological functions in human body by binding to GC receptor (GR), which belongs to the classic steroid receptor superfamily.[9] GR is expressed in most cells of human body, which regulates cellular development, metabolisms, and immune effects.[10] As steroid receptor superfamily protein, GR contains 3 major domains: N-terminal transactivation domain, where it directs GR transactivation function; central DNA binding domain, which exerts its function to binding to GC receptor element (GRE) within nuclear DNA promoter regions; and C-terminal ligand biding domain, which performs GC-activating GR to translocate to the nucleus from the cytoplasm.[10]

GR belongs to transcription factor-nuclear receptor superfamily, with its gene located in the Chromosome 5p31 region expanded with 9 exons.[11] Evidence proved that GR is important for life, as its deletion in Exon 2 leads to abnormal development in GR deficiency, causing HPA axis irregularity to make abnormality in physiological and behavioral development.[12] After all, gluconeogenesis in the liver is manipulated by GR.[13]

2. FUNCTIONAL MECHANISMS OF GR

2.1. Genomic signal pathway

Endogenous GC or synthetic hydrophobic Dexamethasone passes through cell membrane and binds to cytoplasmic GR to translocate into the nucleus. In the absence of steroid, GR, in its inactive status, resides in the cytoplasm and complexes with heat shock protein 90 (hsp90), hsp70, and FKBP52.[11] Once GC

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binds with GR, all heat shock proteins are released to form an active GR complex, which gets translocated into the nucleus, leading to genomic transactivation or suppression.[14]

2.2. Nongenomic signal pathway

GC utilizes the classic GR but only to bind to the cellular membrane, or functionally depends on a nonclassic GR termed as nongenomic signal pathway. The nongenomic action is defined as a rapid onset to bind to the membrane protein and initiate the mechanism without influencing gene expression directly.[15]

3. DEXAMETHASONE APPLIED IN CLINIC MEDICINE

Dexamethasone, originally synthesized from corticosteroid in 1957, functions variously in clinical uses.

3.1. Anti-inflammatory medicine

Patients with autoimmune or inflammatory syndrome such as rheumatoid and bronchospasm can be treated with Dexamethasone owing to its immunosuppressive effects.[16] In clinical application such as eye drops, nasal spray, dental surgery, myocardium response, and broad-spectrum antibiotics, combined Dexamethasone demonstrates an efficient adjuvant therapy to reduce inflammatory response and to achieve healing effects eventually.[17]

3.2. Cancer medicine

In certain hematological malignancy such as myeloma, Dexamethasone is either used as a direct chemotherapeutic agent or combined with another antitumor agent like doxorubicin.[18] Some cancer patients undergoing chemotherapy will receive extra Dexamethasone for counteracting side effects associated with antineoplasm treatment, such as elevation of the ondansetron (5-HT_3 receptor antagonist) to decrease emetic vomiting.[19] The development of edema is counteracted by treating with dexamethasone, in either primary or metastatic brain tumor.[20]

3.3. Endocrine medicine

In most GC-resistant syndromes, dexamethasone can be treated as the first choice. Dexamethasone is applied in response to abnormal syndromes of adrenal insufficiency and Addison's disease.[21]

3.4. Mixed medicine

Potent GC and combined GC/antifungal preparation are important in dermatologic practice.[22] Some ulcer-inhibiting compounds such as Dexamethasone will determine the progression or healing of gastric ulcer.[23]

4. DEXAMETHASONE IN COVID-19

4.1. Primary outcome

The coronavirus-infected respiratory disease is caused by a severe acute respiratory syndrome coronavirus [SARS-CoV2 (2019-nCov)] outbreak at 2019 in Wuhan, China. It soon began to continuously impact our daily life in all aspects, worldwide. In a study on the use of Dexamethasone among hospitalized patients with COVID-19, a lower death rate was reported when compared with the untreated group.[24]

4.2. Secondary outcome

Patients who underwent dexamethasone treatment had a shorter and greater discharge alive within 28 days.[24]

4.3. Third outcome

A lower risk of progression of invasive mechanical ventilation was observed in the dexamethasone-treatment group.[24] The total recovery trials suggest 6 mg per day of Dexamethasone treatment to receive up 10 days less of 28 days hospitalized mortality in COVID-19 patients.[24]

4.4. Mechanisms for COVID-19

The possible mechanism of Dexamethasone for COVID-19 therapy is that it manipulates the human immune system. In patients infected with SARS-COV-2, the white blood cells begin to attack the healthy cells to cause cell damage, which in turn likely triggers the cytokine function to lead to inflammation in the whole body. Eventually, Dexamethasone treatment in COVID-infected respiratory airways can lead to decreased breath inefficiency requiring of oxygen and ventilation, as recorded.[25]

5. PROSPECTIVE

WHO and European Medicines Agency have endorsed the guideline of Dexamethasone for the treatment of COVID-19 in junior (over the age of 12) and adult patients who need the supplement of oxygen therapy with a month intake.[26]

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