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Mini review

Pharmaceutical technology can turn a traditional drug, dexamethasone into a first-line ocular medicine. A global perspective and future trends

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ABSTRACT

Dexamethasone is one of the most prescribed glucocorticoids. It is effective and safe in the treatment of a wide variety of ocular conditions, including anterior and posterior segment inflammation. However, its half-life in the vitreous humor is very short, which means that it typically requires frequent administrations, thus reducing patient adherence and causing therapeutic failure. Innovative dexamethasone delivery systems have been designed in an attempt to achieve sustained release and targeting. The FDA has approved dexamethasone implants for the treatment of macular edema secondary to retinal vein occlusion and posterior segment noninfectious uveitis. Lenses, micro- and nanoparticles, liposomes, micelles and dendrimers are also proving to be adequate systems for maintaining optimal dexamethasone levels in the site of action. Pharmaceutical technology is turning a classical drug, dexamethasone, into a fashionable medicine.

1. Dexamethasone and ocular diseases

Among all the corticosteroids available for the treatment of ocular diseases, dexamethasone (Fig. 1, 9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione) is one of the most prescribed worldwide (Rodriguez Villanueva et al., 2016a). It is used to treat a wide variety of ocular conditions, including diseases of both anterior segment inflammation (such as keratitis, blepharitis, allergic conjunctivitis, anterior uveitis and dry eye) and, recently, posterior segment inflammation (such as intermediary uveitis, choroiditis, panuveitis and macular edema); it is also used to reduce inflammation following various ocular surgeries (Blizzard et al., 2016). For the postoperative management and prevention of corneal graft rejection, dexamethasone is commonly prescribed as an immunosuppressive agent (Pan et al., 2015). It is usually dosed in the form of eye drops, suspensions or ointments (Thakur et al., 2011).

Dexamethasone is a potent glucocorticoid (about 30 times more potent than cortisone), and it is very effective in downregulating the expression of inflammatory cytokines (such as IL-1β, IL-6, IL-10, IL-1RA, TNF-α and IFN-γ), chemokines (CXCL-10 and CCL-5, among others), lipocortin, metalloproteases (such as MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13) and TIMP-1 (Coursey et al., 2015; Bian et al., 2016). Additionally, dexamethasone aids in reducing edema, fibrin deposition, retinal vein occlusion and migration of inflammatory cells (Cholkar et al., 2014). With regard to the mechanism of action, glucocorticoids bind specifically and with high affinity to the intracellular cytoplasmic glucocorticoid receptor α, thereby promoting dissociation from heat shock protein 90 and a subsequent translocation to the nucleus. This complex binds to DNA elements, which results in modified transcription (and thus protein synthesis), interference with upstream signal transduction and modulation of RNA stability (Mogensen et al., 2008). Another major anti-inflammatory mechanism is the glucocorticoid-mediated repression of a whole array of genes. This mechanism can inhibit leukocyte infiltration at the site of inflammation via the suppression of ICAM-1 gene expression, interference in the function of inflammatory response mediators through direct protein–protein interactions between the glucocorticoid–glucocorticoid receptor complex and the transcription factors NF-κB and AP-1, suppression of humoral immune responses, inhibition of blood–retinal barrier breakdown by decreasing the VEGF levels and reduction of inflammation

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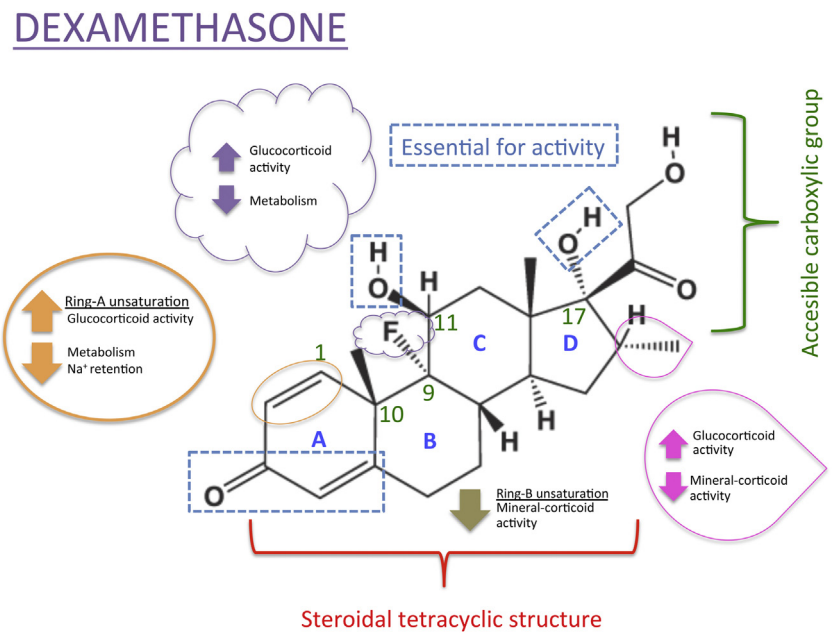

Fig. 1. Analysis of dexamethasone's chemical structure; the requirements for anti-inflammatory action and the opportunities to reduce mineralocorticoid effects are described.

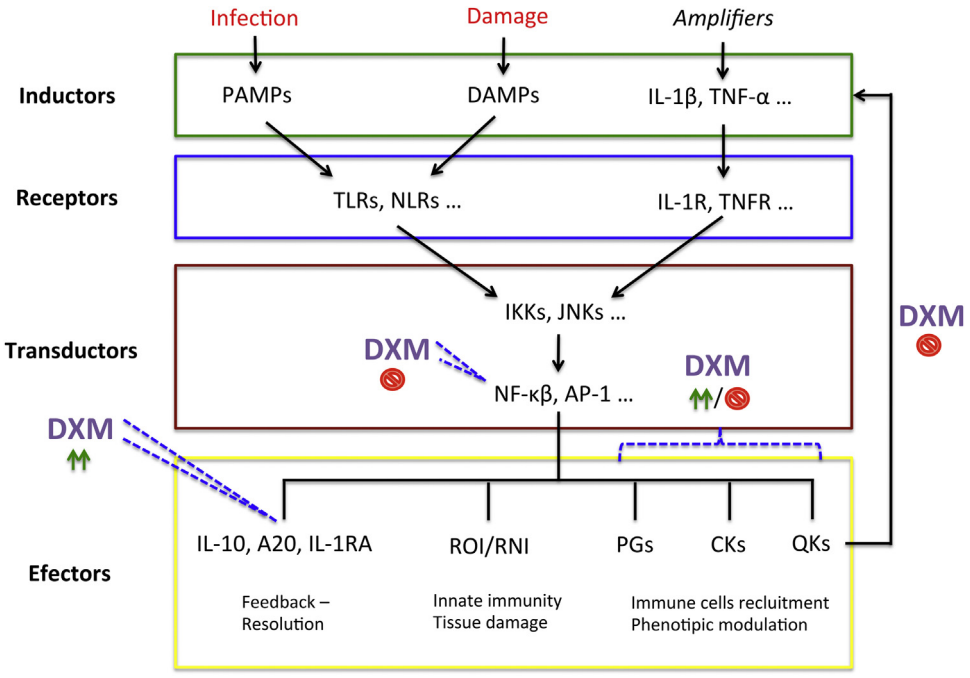

Fig. 2. Outline of the major cellular pathways that inflammation takes after injury or infection and of the steps in which dexamethasone plays an important role. Adapted from Tabas, I. and Glass, C.K. (2013) "Anti-Inflammatory Therapy in Chronic Disease: Challenges and Opportunities," Science, 339, 166–172.

through the NF-κB and MAPK pathways (Prabhu et al., 2015; Figs. 2 and 3).

An effective treatment with dexamethasone needs to achieve and maintain therapeutic concentrations in the target site (Fig. 4). Dexamethasone has been estimated to possess effective anti-inflammatory activity at a concentration of 1000 ng/mL (Barcia et al., 2009). Topical administration of drugs can reach the anterior segment; however, less than 3% of the instilled dose is estimated to reach the aqueous humor (Hughes et al., 2005). This is attributed to the drug's poor permeability across the corneal epithelium (Behl et al., 2016). In the case of a single 50-μl eye drop instillation of a 0.1% mg/ml solution of dexamethasone disodium phosphate, the dexamethasone concentration is measurable in the human aqueous humor within 15–30 min for up to 3–5 h and reaches a peak (57.7 ng/mL) 180–240 min after the administration, with a mean concentration of 31 ng/mL (0.12 nm) (Cagini et al., 2016). Dexamethasone's short aqueous humor half-life of about 3–6 h in solution (Bhagat et al., 2014) makes dosing challenging for many patients because it typically requires frequent administrations (up to 6 times/day), which are subsequently tapered off over several