Journal of Controlled Release xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review

Liposomal corticosteroids for the treatment of inflammatory disorders and cancer

Burcin Ozbakir [a,1], Bart J. Crielaard [a,b,1], Josbert M. Metselaar [d], Gert Storm [a,d,*], Twan Lammers [a,c,d,*]

[a] Department of Pharmaceutics, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands
[b] Division of Pediatric Hematology/Oncology, Weill Cornell Medical College, 515 E71st Street, 10021 NY, USA
[c] Department of Experimental Molecular Imaging, RWTH - Aachen University, Helmholtz Institute for Biomedical Engineering, Pauwelsstrasse 30, 52074 Aachen, Germany
[d] Department of Controlled Drug Delivery, MIRA Institute for Biomedical Engineering and Technical Medicine, University of Twente, 7500 AE Enschede, The Netherlands

ARTICLE INFO

Article history:
Received 9 April 2014
Accepted 20 May 2014
Available online xxxx

Keywords:
Liposomes
Corticosteroids
Nanomedicine
Inflammation
Cancer

ABSTRACT

Glucocorticoids (GC) are known for their potent immunosuppressive and anti-inflammatory properties. As a result, they are extensively used for the treatment of many different diseases. Prolonged and/or high-dose GC therapy, however, generally comes with severe side effects, resulting not only from their very diverse mechanism(s) of action, but also from their relatively poor biodistribution. Drug delivery systems, and in particular liposomes, have been extensively used to enhance the biodistribution and the target site accumulation of GC, and to thereby improve the balance between their efficacy and their toxicity. Many different types of liposomes have been employed, and both local and systemic treatments have been evaluated. We here summarize the progress made in the use of liposomal GC formulations for the treatment of asthma, rheumatoid arthritis, multiple sclerosis and cancer, and we show that the targeted delivery of GC to pathological sites holds significant clinical potential.

1. Introduction

1.1. Liposomes

Ever since their first description by Alec Bangham more than half a century ago, liposomes have been extensively used for drug delivery applications [1–3]. Because of their relatively straightforward preparation, as well as their excellent biodegradability and biocompatibility, liposomal systems have progressed into one of the most extensively used and clinically most advanced drug delivery platforms [4].

Liposomes are composed of phospholipids, which, due to their amphiphilic nature, spontaneously self-assemble into vesicular structures when dispersed in aqueous media. In these lipid vesicles, the hydrophilic head groups line up and face the outer aqueous environment, while another layer of polar heads face the aqueous interior, segregating the hydrophobic tail groups of both layers from the aqueous environment (Fig. 1). The vesicular membrane [2], which in fact may consist of a number of bilayers, provides the liposome with structural stability, and enables the encapsulation of pharmacologically active agents, either in the layer itself for lipophilic compounds, or – more commonly – in the aqueous core for hydrophilic compounds [5]. When administered locally, the liposomal formulation allows for prolonged retention of the encapsulated drug at the injected site by limiting its diffusion and degradation ('depot' function). By limiting renal excretion and hepatic degradation, some liposome formulations, especially those with high transition-temperature saturated phospholipids and high cholesterol content, optionally containing a small percentage of PEGylated lipids (so-called 'long circulating liposomes') improve the pharmacokinetics of encapsulated drugs when administered systemically, allowing them to circulate for prolonged periods of time.

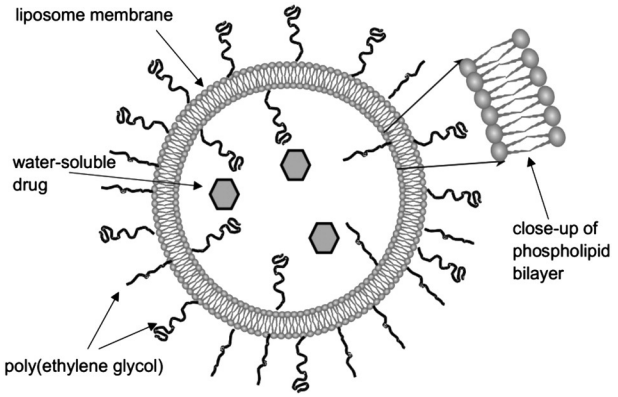
In addition, the 'Enhanced Permeability and Retention' (EPR) effect [7] promotes the accumulation of liposomes in tissues characterized by enhanced vascular leakiness, such as tumors and sites of inflammation, while at the same time attenuating their localization in healthy non-target tissues. In addition, liposomes can also be administered locally, such as through inhalation, and can increase the delivery and accumulation of drug molecules in the target tissue. As a consequence, liposomal drugs tend to be more effective and less toxic than standard (low-molecular-weight) drugs, they can be administered less frequently, and can improve both time- and cost-effectiveness.

1.2. Glucocorticoids

Glucocorticoids (GC) are a class of steroid hormones that possess strong immunosuppressive and anti-inflammatory activity. Ever since their introduction in the 1950s, GC have therefore been extensively used in diseases caused by an excessively active immune system, such as allergies, asthma, autoimmune diseases and sepsis [8]. GC exert

* Corresponding authors.
E-mail addresses: g.storm@uu.nl (G. Storm), tlammers@ukaachen.de (T. Lammers).
[1] These authors contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.jconrel.2014.05.039
0168-3659/



Q2 **Fig. 1.** Schematic depiction of a long-circulating liposome.
Image reproduced, with permission, from [6].

their effects by binding to the glucocorticoid receptor (GR) [9], which, once inside the nucleus, modulates several DNA transcription factors. This leads to the up-regulation of anti-inflammatory protein production and to a concomitant down-regulation of pro-inflammatory protein production (Fig. 2) [10].

In addition to such relatively slow genomic effects, GC also display more rapid non-genomic effects, including e.g. inhibition of arachidonic acid release and alterations in cation transport across the plasma membrane [12]. The genomic and non-genomic effects together, change the metabolism of lipids, carbohydrates, proteins and have been shown to affect bones, neurons, glial cells, and the electrolyte and water balance [7]. Although the glucocorticoid receptor (GR) is involved, the exact molecular mechanism driving the non-genomic activity of GC still remains unclear [7,12,13].

Because of their broad pharmacologic activity, GC are notorious for their side effects. These include immunosuppression (and the increased risk of infection), musculoskeletal complications (such as osteoporosis, osteonecrosis, myopathy), growth suppressive effects (in children), hypertension, rapid weight gain, diabetes, hypertriglyceridemia, hypercholesterolemia, dermatological effects (fat redistribution, thinning of the skin, allergic reactions), glaucoma, peptic ulcer disease, decelerated wound healing, and electrolyte imbalance [7,14].

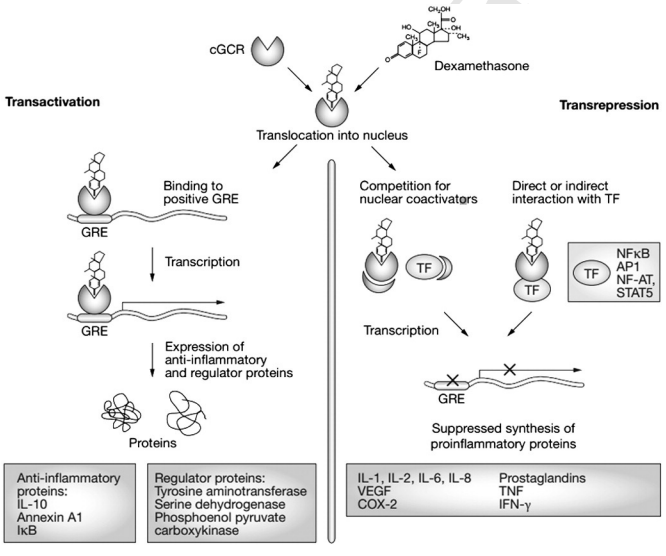


Fig. 2. Mechanism of action of glucocorticoids (GC). Upon binding to the cytosolic glucocorticoid receptor (cGCR), GC activate and repress a large number of important (anti-) inflammatory mediators. Only genomic effects, at the transcriptional level, are shown.
Image reproduced, with permission, from [11].

The encapsulation of GC in liposomes has been extensively evaluated over the past 2–3 decades. This is done to reduce the volume of distribution and the off-target accumulation of GC, thereby lowering their toxicity, as well as to increase and prolong drug levels at the pathological site, to improve their therapeutic efficacy. We here summarize several key advances in this area of research, and provide an overview of studies showing the potential usefulness of liposomal GC for improving the treatment of asthma, multiple sclerosis, rheumatoid arthritis and cancer.

2. Liposomal glucocorticoids for inflammatory disorders

2.1. Asthma

2.1.1. Pathophysiology of asthma and therapeutic role of glucocorticoids

Asthma is a chronic respiratory disorder with a strong allergic component, which is characterized by an obstruction of the pulmonary airways, causing shortness of breath, wheezing, coughing and chest tightness or pain [15]. The disease initially develops with bronchial provocation and hyper-responsiveness, followed by bronchial inflammation and swelling of the inner walls of the airways (lamina reticularis). In addition, increased growth of mucus cells leads to mucus hypersecretion and a thicker mucus structure. This results in an increased tendency to lung hyperinflation, smooth muscle hypertrophy, edema and cilia cell disruption [15]. Although the symptoms of asthma are mostly reversible, the associated inflammation of the pulmonary tract may lead to permanent structural changes, also known as airway remodeling [16].

Asthma therapy generally aims to reduce symptoms, maintain pulmonary function, prevent recurrent exacerbations, and minimize hospitalization [17]. In addition to non-steroidal therapeutics, such as bronchodilators, inhaled glucocorticoids (IGC) are prescribed frequently in asthma therapy, because of their effective anti-inflammatory properties [18]. However, IGC have some limitations due to long-term side effects, especially in older patients [19]. Additionally, with the need of daily dosing, these effects may lead to patient noncompliance and treatment failure. Several studies have demonstrated that the employment of a drug delivery platform for inhaled GC therapy in asthma may have a direct and distinct pulmonary effect with reduced side effects [20–22]. This review focuses on local delivery of liposomes to the lungs for therapy of asthma, which provide an optimized pulmonary residence time of the drug by increasing lung deposition and decreasing upper respiratory tract retention, while drug redistribution to non-target tissues is attenuated [23,24].

2.1.2. Liposomal glucocorticoids for pulmonary therapy of asthma

One of the first clinical studies involving liposomal GC in asthma evaluated the use of nebulizers to administer dilauroyl phosphatidylcholine (DLPC) liposomes containing beclomethasone dipropionate (Bec-DP) [25]. Using 18 different types of nebulizers, the local lung deposition efficiency of liposomes with a diameter of 1–3 μm was evaluated. While the majority of nebulizers were able to provide acceptable performance for delivering Bec-DP liposomes, only two of them, i.e. Aerotech II and Spira, achieved high localization in alveolar airways, and relatively low deposition in mouth and throat.

The lung deposition and clearance of ^{99m}Technetium-labeled Bec-DLPC liposomes was visualized and quantified in a follow-up study [26]. These experiments showed that ~75% of the inhaled liposomes were in the pulmonary tract, ~12% in the nasopharynx, and ~13% in the stomach and intestine (Fig. 3A). Although free ^{99m}Tc was cleared within minutes, ~50% of the liposome-associated radioactivity was still found to be present in the lungs 24 h after inhalation, indicating a substantially prolonged retention of radiolabeled liposomes in the lungs (Fig. 3B).

Also in healthy human volunteers, a strong deposition in the lungs and oropharynx was observed upon using the Aerotech II and Spira