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The novel drug delivery systems in liver dysfunction

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Abstract

The liver is a vital organ present in vertebrates and some other animals. Its wide functions include detoxification, protein synthesis, and production of biochemical necessary for digestion. This organ is necessary for survival. Currently there is no option to compensate for the absence of liver function. Drug targeting for various liver diseases can focus on various cells of liver including kupffer cells, sinusoidal endothelial cells, hepatic stellate cells or hepatocytes. In one or the other diseases, the involvement of these diseases has been clarified. Several diseases afflict liver. The major diseases of liver include HBV infection, liver fibrosis/cirrhosis, hepatocellular cancer. Several cells of the liver which are exposed to blood circulation or not exposed to blood circulation are involved in these diseases. Although conventional routes of administration can lead to drug access into these varieties of cells, means to increase the effectiveness of these by various drug delivery approaches has been attempted recently. This review briefly covers the latest and retrospective drug delivery system approaches published in the scientific literature.

Keywords: Liver; Kupffer cells; Liver fibrosis; Drug delivery system

1. Introduction

The past 30 years have witnessed major progress in the knowledge and management of liver disease[1]. This report reviews several studies published in the last five years to survey the current state of evidence to be able to treat various liver disorders using drug delivery strategies. The incidence and prevalence of two conditions, cirrhosis and primary liver cancer, are key to understanding the burden of liver disease. They represent the end-stage of liver pathology and thus are indicative of the associated mortality. Literature on the prevalence and incidence of cirrhosis and liver cancer is scarce. Data here is illustrated taking Europe's data on cirrhosis and liver cancer. Available data suggest that about 0.1% of the European population is affected by cirrhosis, corresponding to 14-26 new cases per 100,000 inhabitants per year or an estimated 170,000 deaths per year. There are, however, large intra-European variations. About 0.1% of Hungarian males will die of cirrhosis every year compared with 0.001% of Greek females. Hepatocellular carcinoma (constituting 70-90% of cases of primary liver cancer) is the fifth most common cause of cancer in Europe and one of the most serious outcomes of cirrhosis. European epidemiological data show that there are 1-13 new cases of hepatocellular carcinoma and 1-10 deaths per 100,000 inhabitants per year. WHO estimate that liver cancer is responsible for around 47,000 deaths per year in the EU? The four leading causes of cirrhosis and primary liver cancer in Europe are harmful alcohol consumption, viral hepatitis B and C and metabolic syndromes related to overweight and obesity. Chronic alcohol consumption is the main cause of cirrhosis in Europe. Alcohol consumption decreased in the 1990s, but has increased again in the last decade to stabilize at a high level of >9 litres of pure alcohol per year on average, although there are large variations among European countries. Chronic viral hepatitis B is the second major cause of both cirrhosis and liver cancer. Between 0.5% and 0.7% of the European population is affected by chronic hepatitis B, with the highest prevalence being recorded in Romania (5.6%) and Greec (3.4%). By comparison, HIV prevalence is only 0.2% (HIV is 50-100 times less infectious). The availability of a vaccine has resulted in a decrease in

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the prevalence of HBV, although it remains responsible for 30% of cases of cirrhosis and 15% of cases of primary liver cancer. Chronic hepatitis C is an important risk factor for hepatocellular carcinoma, which develops several decades after infection. Since the discovery of the virus in the late eighties, the number of new cases of infection has dropped substantially. Prevalence rates of hepatitis C virus (HCV) infection in the last decade in the European population were between 0.13 and 3.26%, the highest rates being found in Italy and Romania. These HCV –infected populations will develop complications in the years to come, leading to a substantial increase in the burden of disease. It is of great concern that about 90% of people in Europe infected by viral hepatitis are unaware of their status. Non-alcoholic fatty liver disease (NAFLD) is becoming a major concern with the increasing incidence of obesity in Europe. In this condition, accumulation of fat in the liver leads to chronic liver disease. Available data suggest the prevalence rate of NAFLD is 2–44% in the general European population (including obese children) and 42.6– 69.5% in people with type 2 diabetes. NAFLD increases the risk of cirrhosis and liver cancer. Each of these four major causes of liver disease is amenable to prevention and treatment. In many of these conditions liver resection and transplantations are the only options available as of today. Novel therapeutics and drug delivery systems to treat various liver disorders are beginning to emerge. Some of the research works are described in this review.

2. Delivery Systems

2.1. Carbon nanotubes

Carbon nanotubes for Kupffer cell targeting for effective management of cytokine-induce liver damage has been investigated[2]. Sulfasalazine was loaded into the fucosylated MWCNTs after subsequential functionalization (carboxylation, acylation and amidation) using dialysis membrane technique. The in vitro, in vivo studies were performed on macrophages J 774 cell line for Kupffer cells targeting for the treatment of cytokine-induced liver damage. The loading of SSZ into SSZ-FUCO-MWCNTs was 87.77 Â± 0.11% (n = 3). Sustained release was obtained from SSZ-FUCO-MWCNTs, with 89.12 Â± 0.71% of SSZ released into medium at 48th hr. SSZ-FUCO-MWCNTs showed the 9.01 Â± 0.23% hemolysis was drastically reduced from 21.62 Â± 0.24% SSZMWCNTs 21.62 Â± 0.24%. In SRB assay, SSZ-FUCO-MWCNTs showed more cytotoxicity than raw and SSZ-MWCNTs. In cytokine assay, SSZ- FUCO-MWCNTs exhibited significantly higher inhibition of IL-12 p40 secretion. In Western blot assay, SSZ-FUCO-MWCNTs significantly inhibit NF-ÎºB activation. Conclusion: The results suggested that the SSZ-FUCO-MWCNTs may be useful nano-carriers for targeted delivery to Kupffer cells in the treatment of cytokine-induced liver damage.

2.2. Spherical particles

Liver targeting of the drugs, specifically to the Kuppfer cells can be achieved after i.v. administration of drug loaded spherical particles[3]. This mode of administration of drugs enhances its overall delivery to the liver via passive targeting. The purpose of this study was: 1) To optimize pharmacokinetics and kupffer cell (KC) uptake of catechin after i.v. administration of catechin-polycaprolactone nanoparticles and microparticles 2) To optimize particle size for improvement in targeting to the KC with catechin polycaprolactone spherical particles (CSP). A w/o/w solvent evaporation technique was used to prepare CSP and particles were characterized for in vitro parameters, pharmacokinetics (PK) and KC uptake. To optimize the particle size, a series of nano- and micro-particles encapsulating the same drug amounts were investigated for hepatoprotective activity. Ten different CSP of sizes ranging from 200 nm to 25 pim were successfully prepared. PK parameters suggested that nanoparticles offered better PK and enhanced KC uptake compared to microparticles. Nanoparticles resulted in better hepatoprotection in CCl4 induced liver fibrosis model compared to microparticles (Hepatoprotection rank: 365 nm > 1.1 pim > 3.2 pim = 6.1 Î¼m < 10.4 pim) suggesting that liver uptake, particularly KC uptake is more with nanoparticles. Particles of sizes greater than 6 pim lead to reduction in liver uptake and increase in lung uptake. The study concludes that nanoparticules are better and optimized for catechin delivery to KC compared to micro particles.

2.3. Radionuclide imaging

Radionuclide imaging of molecular targets for cancer therapy is likely to be a powerful tool for patient stratification and response monitoring, allowing more personalized cancer treatment[4]. Radiolabeled proteins and peptides are a promising class of imaging probes for visualization of molecular targets in vivo. However, hepatic uptake and hepatobiliary excretion of radioactivity can decrease imaging contrast, reducing the detection sensitivity of hepatic and extra hepatic abdominal metastases, respectively. In this article, we review factors that influence the hepatic uptake of radioactivity (e.g. the chemical nature of radiocatabolites and physicochemical properties of targeting peptides and linkers) to provide input for the rational design of peptide-based imaging probes.

2.4. Antisense technology

Novel therapeutics using antisense technology requires an efficient and safe delivery system with Kupffer cell targeting ability[5]. The capacity of galactosylated low molecular weight chitosan (GLC) to efficiently mediate the antisense oligonucleotide (ASO) TJU-2755 into Kupffer cells, enhance the effect of the oligonucleotides on the suppression of tumor necrosis factor (TNF)-Î± and prolong the active time of the antisense drug in vivo was investigated. The protective and therapeutic effect of ASO/GLC in the animal model of D-galactosamine/lipopolysaccharide-induced fulminant hepatitis was tested. ASOs delivered by GLC were concentrated in Kupffer cells and more potent in reducing the expression of TNF-Î± mRNA, as well as reducing serum TNF-Î± levels. Furthermore, the ASO/GLC complex successfully rescued animals from fulminant hepatitis and mortality. Compared to naked ASO, the complex notably reduced the dose administrated in animals and prolonged its effectiveness. A single dose of 5 mg ASO per kg body weight achieved a satisfactory effect after 5 days, and 20 mg ASO per kg body weight preserved 70% of the effect after more than 2 weeks. Its efficacy was affirmed through both pretreatment and therapeutic use after liver damage had begun. Conclusions: Inhibiting TNF-Î± expression in the liver by this strategy represents a novel therapeutic approach that may be valuable for the treatment of some inflammation-related liver diseases.

2.5. Superparamagnetic iron oxide nanoparticle (SPIO)

Superparamagnetic iron oxide nanoparticle (SPIO) stabilized with alginate (SPIO-alginate), and investigate its potential in detecting liver cancers as a newly developed magnetic resonance (MR) contrast agent[6]. Pharmacokinetics and tissue distribution of SPIO-alginate were investigated in Sprague-Dawley rats. The results showed that SPIO-alginate was eliminated rapidly from serum with the half-life of 0.27 h at 109.5 Î¼mol Fe/kg and accumulated dominantly in liver and spleen with a total percentage of more than 90% of dose after intravenous injection. The studies of pharmacokinetics and distribution of SPIO-alginate in rats indicated the MR contrast agent, based on SPIO, mainly accumulating in targeting organs that contain phagocytosing cells, i.e. liver and spleen. The efficacies in detecting hepatocellular carcinoma (HCC) of rat with primary liver cancer and xenograft liver cancers of rabbit were investigated before and after injection of SPIO-alginate. The signal intensity of liver parenchyma in rabbit with VX2 tumor after injection of SPIO-alginate was reduced sharply resulting in a significant contrast between liver parenchyma and tumor. Detection of the HCC in rat model was also demonstrated. The present study provides evidence that SPIO-alginate might have the ability to improve the detection of liver tumors as an MR contrast agent, and the efficacy is associated with the SPIO specifically located in Kupffer cells in hepatic sinusoid.

2.6. Drug carriers

The most relevant target cells are identified for each liver disease and the strategies for drug delivery to these cells are subsequently reviewed[7]. The review describes the use of proteins, viruses, polymers and liposomes for therapeutic purposes in various liver diseases. It is shown that to date, all resident intrahepatic cells can be reached with several different drug carriers. Much progress has been made in recent years to deliver small drug molecules, proteins and nucleic acids specifically to the key pathogenic cells in vivo. The knowledge of drug targeting gained in the past decades, combined with a proper preclinical evaluation, may bring new therapeutics to the clinic in the near future.

2.7. The role of Tacrolimus in liver transplantation

Tacrolimus is a potent immunosuppressant used in liver transplantation to avoid graft rejection. Tacrolimus has a narrow therapeutic index and variable pharmacokinetics, making dose adjustment and therapeutic drug monitoring a complicated task[8]. Increasing the occurrence of adverse effects, especially nephrotoxicity are another concerns. In graft rejection, antigen presentation occurs in the graft and lymphatics. Therefore, by targeting tacrolimus to the liver and spleen, graft survival could be achieved with a decrease in nephrotoxicity[8]. Poly (lactide) tacrolimus nanoparticles (PLA-TAC-NP) were formulated and characterized with the aim of targeting tacrolimus to the liver and spleen and therefore decreasing its nephrotoxicity. To evaluate the targeting efficiency of PLA-TAC-NP, rats were divided into two groups. They were intravenously injected either PLA-TAC-NP or free tacrolimus. At assigned time intervals, blood, liver, spleen and kidney samples were collected from each rat. . Drug extraction and HPLC analysis were used to evaluate tacrolimus tissue distribution and consequently the targeting efficiency of the prepared PLA-TAC-NP. PLA-TAC-NP proved their success in targeting liver and spleen, by showing significantly higher drug amounts compared to the rats injected with free tacrolimus. PLA-TAC-NP increased tacrolimus concentration in the liver 24 fold and in the spleen 1.94 fold whereas tacrolimus concentration in the kidneys decreased by 7.12 fold. Transmission electron microscopy (TEM) was used to examine a liver section, obtained from a rat that has received PLA-TAC-NP. TEM images showed PLA-TAC-NP in a Kupffer cell and in the liver sinusoids. Therefore, PLA-TAC-NP are promising drug delivery systems for achieving localized immunosuppression and minimizing nephrotoxicity in liver transplant patients.

2.8. Hepatic stellate cells (HSC)

Hepatic stellate cells (HSC) play a critical role in the fibrogenesis of liver, so they are the target cells of antifibrotic therapy[9]. Several kinds of targeted delivery system that could target the receptors expressed on HSC have been designed, and have shown an attractive targeted potential in vivo. After being carried by these delivery systems, many agents showed a powerful antifibrotic effect in animal models of liver fibrosis. These targeted delivery systems provide a new pathway for the therapy of liver fibrosis.

2.9. Therapeutic genes or drugs at target site

Delivery of therapeutic genes or drugs should be targeted to either one of the following cells in the liver: hepatocytes, Kupffer cells and tumor endothelial cells, or to the tumor cells themselves[10]. To maximize the therapeutic effect and minimize systemic toxicity or nontarget injuries, the sufficient amount or dose of genes or drugs should be specifically delivered to a target, with minimal exposure in their active forms to nontarget cells. There are diverse strategies to improve selective delivery or targeting efficiency.

2.10. Anti-fibrogenic therapies

Anti-fibrogenic therapies have been shown to be effective in experimental animal models; licensed therapies have yet to emerge[11]. A potential problem for any anti-fibrogenic therapy in the liver is the existence of the body's major drug metabolising cell (the hepatocyte) adjacent to the primary fibrosis-causing cell, the myofibroblast. The development of a human recombinant single-chain antibody (scAb) that binds to the surface of myofibroblasts. This antibody binds specifically to myofibroblasts in fibrotic mouse livers. When conjugated with a compound that stimulates myofibroblast apoptosis, the antibody directs the specific apoptosis of myofibroblasts with greater specificity and efficacy than the free compound. The antibody also reduces the adverse effect of liver macrophage apoptosis and-in contrast to the free compound-reversed fibrosis in the sustained injury model used. These data suggest that specifically stimulating the apoptosis of liver myofibroblasts using a targeting antibody has potential in the treatment of liver fibrosis.

2.11. Low molecular weight chitosan (gal-LMWC)

The gal-LMWCs preference for Kupffer cells was confirmed by *in vivo* and *in vitro* experiments[12]. Furthermore, asialoglycoprotein receptor (ASGPr) was studied as a possible surface lectin which may involved in the endocytosis of the gal-LMWC/ODN complexes. Results showed that the gal-LMWC/ODN complex accumulated in liver when injected intravenously (i.v.). Further studies revealed that 50.6% of the complex was taken up by Kupffer cells in liver, 33.2% was taken up by endothelial cells, and only 16.2% of the complex was taken up by parenchymal cells. In vitro results also confirmed the affinity of gal-LMWC to murine Kupffer cells. Inhibition of the transfection by lactose and N-acetyl galactosamine (GalNAc) suggested that the particles might enter macrophages via ASGPr and the inhibition by LMWC implied that there might be other lectins involved in the endocytosis.

2.12. Mannosylated and fucosylated proteins

Mannosylated and fucosylated proteins in primary cultured sinusoidal endothelial cells and Kupffer cells were investigated[13]. In cultured sinusoidal endothelial cells, uptake of mannosylated and fucosylated bovine serum albumin (BSA) was significantly inhibited by excess mannosylated and fucosylated BSAs but not by galactosylated BSA, suggesting that both glycosylated proteins might be primarily taken up via mannose receptors. In cultured Kupffer cells, uptake of fucosylated BSA was significantly inhibited by excess galactosylated BSA as well as mannosylated and fucosylated BSAs, although that of mannosylated BSA was inhibited only by mannosylated and fucosylated BSAs. This suggests that uptake of fucosylated BSA by Kupffer cells might be mediated by both Kupffer cell lectin (fucose receptor) and mannose receptor. On the other hand, in vivo hepatic uptake of fucosylated BSA was inhibited to a greater extent by GdCl 3 pretreatment than that of mannosylated BSA. Based on in vitro and in vivo experiments, it was concluded that fucosylated BSA is more Kupffer cell-selective because it exhibited a lower sinusoidal endothelial cell uptake than mannosylated BSA.

2.13. Immunonanoparticles

Immunonanoparticles with complete antibody (Wab - DRB - HSA - NP), immunonanoparticles with F (ab) 2 fragments [WF(abâ€²) 2 - DRB - HSA - NP] were investigated for their targeting to tumor[14]. Hetero-bi-functional cross-linker SPDP was used to couple anti-Walker-256 cells polyclonal antibodies (Wab) or its F(abâ€²)2 fragment [WF(abâ€²)2] with doxorubicin - loaded human serum albumin nanoparticles (DRB-HSA-NP) The targeting of nanoparticles (DRB-HSA-NP) and two kinds of immunonanoparticles to carcinoma cells was studied in vitro and in vivo. Compared with DRB - HSA - NP, both kinds of immunonanoparticles could efficiently bind to Walker - 256 cells in vitro. Although only a few

of immunonanoparticles was detected in tumor tissue after administration via tail vein, the immunonanoparticles were mainly accumulated in tumor after intra - tumor administration.

2.14. Human serum albumin (Dexa10-HSA)

Dexamethasone (Dexa) was coupled to human serum albumin (Dexa10-HSA) for the targeting of this anti-inflammatory drug to Kupffer cells (KC) and sinusoidal endothelial cells (SEC) in the liver: key players in the pathogenesis of acute and chronic inflammatory liver diseases like fibrosis[15]. Cell-specific delivery of Dexa may increase its efficacy and prevent side effects. We, therefore, studied the pharmacokinetic profile, efficacy, and toxicity of Dexa10-HSA in bile duct ligation (BDL)-induced fibrosis in rats. Dexa10-HSA was taken up by scavenger receptors on KC and SEC and was rapidly cleared from the blood stream, with no differences in kinetic parameters between normal and fibrotic rats. KC isolated from livers of rats treated with Dexa10-HSA was unresponsive to lipopolysaccharide in contrast to controls. A dose of 0.1 mg kg-1 three times a week reduced intrahepatic reactive oxygen species production strongly as compared to untreated BDL rats. This dose, however, also stimulated the depositions of collagens I and III. Overdosing of Dexa10-HSA (10 mg kg-1) led to a lethal reduction of body and spleen weight.

2.15. Cytokines

During proinflammatory reactions such as endotoxemia, ischemia-reperfusion and immune reactions, excessive amounts of cytokines and prostanoids are released resulting in liver injury. In the liver, Kupffer cells are the primary source of cytokines and prostanoids. Obliteration of Kupffer cells prevents experimentally-induced liver damage, suggesting a major role for Kupffer in the pathogenesis of liver diseases. Pretreatment of experimental animals with antibodies directed against cytokines such as tumor necrosis alpha (TNF-alpha) prevented experimentally-induced liver damage. In recent years, antisense oligonucleotides (ASOs) directed against specific mRNAs has been tested as an alternative therapy to control the excessive production of inflammatory peptides. Although ASOs have great potential against gene expression, their design, in vivo delivery and stability, have posed significant challenges. Computer-aided configurational analysis and identification of viable motifs (GGGA) on the pre-mRNA transcripts have, in part, alleviated the problems in designing effective ASOs. However, the major challenge involves the in vivo delivery of an ASO to the target tissue. Additionally, it is critical that once taken up by the cells, the ASO is able to survive the lysosomal barrier and enter the cytoplasm. Anionic liposomes and lactosylated low-density lipoproteins (LDL) have been successively used as adjuvants for delivery of ASOs to Kupffer cells[16].

2.16. Immunoliposomes

Specific targeting of drugs to for instance tumors or sites of inflammation may be achieved by means of immunoliposomes carrying site-specific antibodies on their surface. The presence of these antibodies may adversely affect the circulation kinetics of such liposomes as a result of interactions with cells of the mononuclear phagocyte system (MPS), mainly represented by macrophages in liver and spleen. The additional insertion of poly (ethylene glycol) chains on the surface of the immunoliposomes may, however, attenuate this effect. We investigated the influence of surface-coupled rat or rabbit antibodies and of PEG on the uptake of liposomes by rat Kupffer cells in culture with 3H-cholesteryloleyl ether as a metabolically stable marker. Additionally, we assessed the effects of surface-bound IgG and PEG on the intracellular processing of the liposomes by the Kupffer cells, based on a double-label assay using the 3H-cholesteryl ether as an absolute measure for liposome uptake and the hydrolysis of the degradable marker cholesteryl-14C-oleate as relative measure of degradation. Attachment of both rat and rabbit antibodies to PEG-free liposomes caused several-fold increase in apparent size. The uptake by Kupffer cells, however, was 3-4 fold higher for the rat than for the rabbit IgG liposomes. The presence of PEG drastically reduced the difference between these liposome types. Uptake of liposomes without antibodies amounted to only about 10% (non-PEGylated) or less (PEGylated) of that of the immunoliposomes. In contrast to the marked effects of IgG and PEG on Kupffer cell uptake, the rate of intracellular processing of the liposomes remained virtually unaffected by the presence of these substances on the liposomal surface. These observations are discussed with respect to the design of optimally formulated liposomal drug preparations, combining maximal therapeutic efficacy with minimal toxicity[17].

2.17. Dexamethasone coupled mannosylated albumin (Dexa 5-Man 10-HSA)

Dexamethasone coupled to mannosylated albumin (Dexa 5-Man 10-HSA) was designed by us to selectively deliver this anti-inflammatory drug to the KC. The effectiveness of Dexa 5-Man 10-HSA was studied both in organ cultures and fibrosis induced by bile duct ligation (BDL) in rats. Dexa 5-Man 10-HSA accumulated in livers of both healthy and fibrotic rats (67%Â±5% and 70%Â±9% of the dose, respectively) and uptake was found almost exclusively in KC. Active dexamethasone was liberated from its carrier, because Dexa 5-Man 10-HSA could effectively inhibit nitric oxide (NO) and tumor necrosis factor Î± (TNF-Î±) release in endotoxin-activated liver slices. In vivo, however, this was associated with increased collagen I and III depositions and enhanced tissue inhibitor of metalloproteinase-1 (TIMP-1) mRNA

expression. This was accompanied by a decreased influx of reactive oxygen species (ROS) producing cells in the livers of BDL animals treated with Dexa 5-Man 10-HSA as compared with untreated BDL rats. Dexa 5-Man 10-HSA treatment also replenished the depleted glycogen stores in hepatocytes of BDL livers. In conclusion, our studies showed selective delivery of dexamethasone to KC with Dexa 5-Man 10-HSA. This conjugate reduced intrahepatic ROS in vivo and TNF-Î± production in vitro and prevented glycogen depletion in vivo, indicating effective pharmacologic targeting[18].

2.18. Poly (D,L-lactide-co-glycolide) (PLGA) nanoparticles

Poly (D, L-lactide-co-glycolide) (PLGA) nanoparticles of 150-nm mean size were produced by an interfacial deposition method. The polar model drug Rose Bengal was successfully loaded into the nanoparticles during production and the surface of these particles was subsequently modified with poloxamer 407 and poloxamine 908 in order to create a steric stabilising layer of PEG on the surface. Drug loading was low (<1%) which can be attributed to the polar nature of the drug and the small size of the nanoparticles. Drug release was biphasic with 50% release measured within 30 min in serum. After intravenous injection in rats, the drug loaded nanoparticles substantially avoided capture by the Kupffer cells of the liver as compared to free drug. The half-life of Rose Bengal in the blood stream when administered in the nanoparticles was greatly extended with âˆ¼30% remaining after 1 h as compared to only 8% of Rose Bengal left 5 min after administration in solution. These surface modified nanoparticles would have potential as carriers for drugs to specific sites within the body or for slow release of drug within the circulation[19].

2.19. Mannosylated bovine serum albumin (Man-BSA)

Mannosylated bovine serum albumin (Man-BSA) were pharmacokinetic ally investigated. After intravenous injection, 111In-Man18-BSA accumulated in the liver up to 70% of dose at 2 h; the endothelial cells and Kupffer cells contributed about 66% and 21% of the uptake, respectively. In single-pass perfusion experiments using rat liver at varying inflow concentrations (0.1-2.0 Î¼g/ml), 111In-Man18-BSA and 111In-Man33-BSA were continuously extracted by the liver and their extraction ratios decreased with the increasing inflow concentrations. The outflow curves of each 111In-Man-BSA at three concentrations were simultaneously fitted to a pharmacokinetic model including a binding to the cell surface and internalization, by using a nonlinear regression program MULTI (RUNGE). The binding constant augmented with the increase in the number of mannose per BSA, whereas the internalization rate constant was quite comparable for both derivatives. The pharmacokinetic analysis has demonstrated that the uptake process of 111In-Man-BSA is characterized to possess fewer binding sites and a greater internalization rate in comparison with other liver-specific carriers such as galactosylated, succinylated and cationized BSAs. These results will provide useful information in designing drug targeting systems to the liver nonparenchymal cells via mannose receptors[20].

2.20. Antisense oligonucleotides

A targeted delivery of antisense oligonucleotides into Kupffer cells might reduce or prevent liver injury. In this report, we describe a method in which anionic liposome-encapsulated antisense phosphorothioate oligodeoxynucleotides (S-Oligos) are delivered to Kupffer cells in vivo. Delivery was assessed using an antisense S-Oligo (TJU- 2749) targeted against the 3' untranslated region of rat tumor necrosis factor-Î± mRNA. At 90 min postintravenous injection, 90% of the S-Oligo was absorbed from circulation. Of this, 40% was found in the liver and 10% in spleen. Other organs, including lungs, kidneys, muscle, stomach, brain, testes and small intestine, showed only minor incorporation (<5%). Greater than 65% of the liver-associated S-Oligo was found in Kupffer cells. Relative accumulation of S-Oligo in Kupffer cells was 200-fold that of the combined body tissues. For an average injected dose of 1.2 mg antisense/Kg body weight, the intracellular concentration of the S-Oligo attained in Kupffer cells was 65 Î¼M. These studies suggest that liposome-encapsulated delivery provides an efficient means of targeting antisense molecules to Kupffer cells in vivo[21].

2.21. Naproxen (NAP)

Endotoxin is thought to play a major role in cirrhotic liver disease. Cyclo-oxygenase inhibitors were shown to be partially protective against endotoxin but cannot be used in cirrhotic patients because of renal side- effects. We argued that administration of naproxen (NAP) linked to human serum albumin (HSA), which results in specific delivery of NAP to endothelial cells (EC) and Kupffer cells (KC) and exhibited hepatoprotective effects against lipopolysaccharide (LPS) in vitro, could protect cirrhotic rats from LPS toxicity while preserving renal function[22]

2.22. Polyaconitylated HSA (Aco-HSA) liposomes

Human serum albumin (HSA) derivatized with cis-aconitic anhydride was covalently coupled to liposomes with a size of approximately 100 nm [polyaconitylated HSA (Aco-HSA) liposomes]. Within 30 min after injection into a rat, Aco-HSA liposomes were completely cleared from the blood and almost exclusively taken up by the liver, whereas in control liposomes 80% was still present in the blood at that time. Endothelial cells were shown to account for almost two-thirds

of the hepatic uptake of the Aco-HSA liposomes, the remainder being recovered mainly in the liver macrophages (Kupffer cells). With fluorescently labeled liposomes it was shown that the Aco-HSA liposomes target a vast majority (>85%) of the cells in the endothelial cell population. Control liposomes were not taken up to a significant extent by the endothelial cells. Uptake of Aco-HSA liposomes by both endothelial and Kupffer cells was inhibited by preinjection with polyinosinic acid, indicating the involvement of scavenger receptors in the uptake process. The uptake of Aco-HSA liposomes by liver endothelial cells was dependent on liposome size; with increasing liposome diameter endothelial cell uptake decreased in favor of Kupffer cell uptake[23].

2.23. Lipid microspheres (LM)

Lipid microspheres (LM) are a superior carrier for use as a drug delivery system (DDS) due to their high stability and safety. The distribution of LM and the incorporated drugs was investigated in vitro and in vivo. An in vitro study showed that LM were taken up by activated macrophages, neutrophils, vascular endothelial cells, tumor cells, hepatic Kupffer's cells and splenic macrophages. LM accumulated in the vascular lesions of spontanously hypertensive rats after intravenous administration. Moreover, 99mTc-labeled LM accumulated in the inflammatory lesions of patients with rheumatoid arthritis or in the vascular lesions of patients with arteriosclerosis obliterans. Confocal laser imaging showed that PGE1 incorporated into LM targeted the vascular lesions in a patient with Buerger's disease after intravenous injection. Preparations in which drugs are incorporated into LM show a more potent pharmacological activity than the parent compounds because of the targeting effect of LM. Lipid microspheres (LM) are a superior carrier for use as a drug delivery system (DDS) due to their high stability and safety. The distribution of LM and the incorporated drugs was investigated in vitro and in vivo. An in vitro study showed that LM were taken up by activated macrophages, neutrophils, vascular endothelial cells, tumor cells, hepatic Kupffer's cells and splenic macrophages[24].

2.24. Poly (DL-lactide-co-glycolide) PLAGA (50/50) microspheres

Poly (DL-lactide-co-glycolide) PLAGA (50/50) microspheres containing an antineoplastic drug, 5-fluorouracil (5-FU) were prepared by a solvent evaporation process in order to passively target liver carcinomas. The microspheres were spherical with diameters 2-5 Î¼m and encapsulated more than 70% (w/w) of the 5-FU. In vitro release patterns of 5-FU from microspheres were determined for various systems. It was found that drug release depended upon the amount of entrapped drug, the polymer molecular weight and pH of the dissolution medium. The in vitro release mechanism was diffusion controlled and followed a square-root of time relationship. In vivo distribution of 99mTc labeled microspheres after intravenous injection into mice was characterized by an initially high uptake by organs of the mononuclear phagocyte system (MPS). Following i.v. administration of fluorescein-labeled PLAGA microspheres, accumulation was into the MPS, mainly the Kupffer cells cytoplasm and near the liver sinusoids[25].

2.25. Liposomes

Liposome delivery to the liver shows the availability of many therapeutic and scientific opportunities for the use of liposomes in studies of liver physiology and pathophysiology. With liposomes' inherent affinity for the liver, targetability is easily achieved, and as demonstrated by several investigators, parenchymal cell function can be affected. In addition to this, liposomes can accommodate a variety of effector molecules, both lipophilic and hydrophilic. One can envision the incorporation of a variety of molecules in the same liposome preparation, thus maximizing therapeutic value. Additionally, liposomes provide several avenues to study liver function and, of course, therapeutic strategies. Liposomes can easily incorporate fluorescent and/or radiolabel. The inclusion of these marker molecule provide valuable information as to the location and distribution of the injected agent [26.]

3. Conclusion

Liver targeting is a very interesting area in drug delivery. Several cells are involved in the diseases of liver. Targeting these cells can be achieved by a variety of drug delivery approaches. Some of the research works related to liver targeting published in the literature for the last few years have been covered in this review.

Compliance with ethical standards

Disclosure of conflict of interest

All authors do not have any conflict of interest.

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