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Kidney-Specific Drug Delivery: Review of Opportunities, Achievements, and Challenges

Abstract

Kidneys are involved in essential complex procedures that maintain the body in equilibrium and preservethe interior environment necessary for life. Nephritis and nephrosis were ranked among the leading causes of death in all ages in the last global burden of disease assessment of the World Health Organization (WHO). Regarding kidney disease therapeutics, the unfavourable extra-target effects, the narrow therapeutic index, the inactivation of the drug before reaching its target, or the affected normal distribution due to the pathophysiology of diseases, all of these conducted to the requirement of new therapeutic aspects. An efficient kidney-specific drug delivery system will serve as fascinating approach and attractive option conquering such problems, improving the therapeutic index, and direct to a favourable pharmacokinetic profile of drugs. Such breakthrough in renal targeting will provide an efficacious major key for controlling the incidence of those problems, affording a logical treatment methodology managing all at-risk patients, representing a major intention for therapy and impart an attractive pharmacological implement to elucidate the mechanisms of drug action in the kidney.Several attempts to achieve the optimal renal delivery systems had been investigated; low-molecular-weight-proteins (LMWPs), low-molecular-weight chitosan (LMWC), Poly(vinylpyrrolidone-co-dimethyl maleic acid) (PVD), anionized polyvinylpyrrolidone (PVP), galectin-3 carbohydrate recognition domain (G3-C12), and most recently epsilon poly-L-lysine-derivatives (εPLL) and the carrier peptide (KKEEE)3K. The majority of kidney-specific delivery systems target the proximal tubular cells. The specific uptake of the carriers by renal proximal tubular cells is attributed in many cases to megalin-mediated endocytosis. Moreover, the overall charge of the carrier seems to play a key role in kidney-specific drug delivery. On the other hand, mesangial cells represent a particularly suitable target for drug delivery by particulate drug delivery systems such as nanoparticles or liposomes taking into account the particle diameter. In this review, we summarize briefly the aforementioned issues.

Keywords: Renal targeting; Renal proximal tubule cells; Megalin; Mesangium

Review Article

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Abbreviations: WHO: World Health Organization; KD: Kidney Diseases; DDS: Drug Delivery System; LMWP: Low-Molecular-Weight-Proteins; ADEPT: Antibody-Directed Enzyme Prodrug Therapy; PEG: Polyethylene Glycol; PLL: Poly-L-Lysine; LDL: Low-Density Lipoproteins; HDL: High-Density Lipoproteins; PLGA: Poly(D,L-Lactic-Coglycolic-Acid); FDA: Food and Drug Administration; CKD: Chronic Kidney Diseases; ADPKD: Autosomal Dominant Polycystic Kidney Disease; LMWC: Low Molecular Weight Chitosan; PVD: Poly(vinylpyrrolidone-co-dimethyl maleic acid);PVP: polyvinylpyrrolidone;DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; εPLL: Epsilon Poly-L-Lysine; OX7-IL: liposomes with $F_{ab'}$ fragments of OX7 mAb

Introduction

Drug targeting

Drug-targeting aims at reducing the obstacles caused by extra-target effects, the narrow therapeutic index and the inactivation of the drug before reaching its target. Unfortunately, most of the pharmaceutics used today lack a selective delivery into their target tissues. The selective delivery or selective activation in the targeted tissue minimizes toxic side effects [1]. The improvement of the pharmacokinetic profile should be accomplished by drug targeting strategies [2,3]. However, diverse drug-targeting concepts have been pinpointed in order to fulfill those principles [4,5].

Prodrugs are derivatives of drug molecules that undergo an enzymatic or chemical transformation *in vivo* to release the active parent drug, which can then exert the desired pharmacological effect [6]. Therefore, the main idea here is the selective liberation of the pharmacological active part of the prodrug in the target tissue depending on tissue-specific metabolic pathways such as tissue-specific enzyme-depending release [7], altered physiological characteristics such as pH sensitive conjugates [8], agents activated by hypoxia [9], or antibody-directed enzyme prodrug therapy (ADEPT) [10]. In drug delivery, the achievement of tissue-selective or site-selective drug delivery systems (DDSs) is of great interest particularly in the prodrug-based approach [6,11].

Drug delivery systems

A variety of carriers such as viral vectors [12], colloidal particles or macromolecular carriers (such as liposomes [13], nanoparticles [14], microspheres [15], lipid particles and polymeric micelles [16-18]), modified-plasma proteins, polysaccharides [19], biodegradable carriers [20], dendrimers [21], antibodies [22], and peptide carriers have been developed [23].

A large diversity of drug delivery systems has been developed to enhance the therapeutic effect in the target tissue. The exclusive transfer of a drug to the targeted site of action that has been accomplished with minimal toxic side effects, and the usage of a pharmacologically inactive vector are main features of an ideal carrier for drug-targeting delivery system [24]. A specifically targeting drug delivery system can serve not only as a therapeutic vehicle but also as a research tool. Generally, the drug-targeting approach depends on the drug to be delivered, the target tissue, and of course the proper delivery system.

Carriers could be classified into three major types; the particle-type, the soluble and the cellular carriers. Liposomes, nanoparticles, microspheres, lipid particles, and polymeric micelles are all included in the particle-type carriers. Whereas peptides, modified-plasma proteins, polysaccharides, and biodegradable carriers are classified under soluble carriers. However, viral vectors belong to the cellular carriers. Despite the advantages provided by the cellular carriers depending upon their natural biocompatibility and their possibility to cause an immunological response is still a hurdle.

Polymers could be classified according to their natural or synthetic origin, stability (whether biodegradable or not), backbone, and upon their chemical nature (vinyl and acrylic polymers, polyethylene glycol (PEG), polysaccharides, polyamino acids, etc).[8] The natural polymer carriers include several polysaccharides (dextrans, inulin, or chitosan), proteins (albumin) or glycoproteins (transferrin), as well as cationic polymeric carriers such as PLL (poly-L-lysine) backbones [25].

In addition to the size of liposomes (ranging from 20 to 10,000 nm), factors such as charge and lipid composition can extensively dominate their behavior *in vivo*. Liposomes are exploited for macrophage-specific delivery thus involved in passive drug targeting which permits the sustained release of drug over time. Usually, modifications of the surface by a targeting device, homing ligand, or by PEGylation improve their *in vivo* behaviors [26,27]. Size-expansion strategies limit their extravasation, thereby minimizes the drug distribution to non-target sites. PEGylation is involved in the prolonged circulation time of liposomes by preventing their recognition by phagocytes and increasing their peripheral distribution [28].

Similar principles could be achieved depending on the endogenous lipid particles such as low- or high-density lipoproteins (LDL/HDL) which can serve as "natural targeted liposomes" [29]. New applications and opportunities for intracellular delivery of various molecules such as small interfering ribonucleic acid (siRNA), antisense oligonucleotides (ASOs), recombinant proteins and cloned genes, have been achieved through advances in liposome design. In addition, several studies have been performed on the delivery of anti-fungal, anti-viral and anti-cancer drugs by liposome formulations in humans; such as amphotericin B, acyclovir and doxorubicin, respectively. On the other hand, several challenges and obstacles are yet to be faced and defeated; high production costs, short half-life, low solubility, and the possibility of encapsulated drug's leakage and fusion [30].

Nanoparticles and microspheres can be assigned either to the soluble or to the particle type carriers. The main backbone of these carriers is based on diversity of polymers such as dextran, ficoll, sepharose, or PLL. Nowadays, poly(D,L-lactic-co-glycolic-acid) (PLGA) microspheres have been widely studied to gain a wide acceptance for application as nanoparticles and microspheres following to their approval for use in humans by the American Food and Drug Administration (FDA) [31]. Parenteral application of microspheres and nanoparticles for the cell selective delivery of drugs is not the only administration route since they have been studied more recently for their application in oral and pulmonary delivery of peptides and peptidomimetics [20]. Antibodies are aimed at targeting tumor-associated antigens that are over-expressed by tumor cells. Therefore, the birth of new techniques such as recombinant DNA and protein engineering has led to the development of optimal tailored-antibodies [22]. The stretch of amino acids or peptides, contained by a biomolecule which is responsible for specific receptor binding, is called the homing-ligand. Their covalent attachment to a carrier backbone can result in targeted DDS [32]. Polymeric micelles are small (10-100nm) in size and they have a core-shell structure. In contrast to their hydrophobic core, the shell represents their hydrophilic part. Micelles provide a penetration property inside the tissue for targeted DDS. Generally, their utility is still challenging since they disintegrate rapidly *in vivo* [33]. Usually, the application of peptide carriers requires an over-expressed receptor and sufficient *in vivo* stability. Additionally, the conjugated drug should not interfere with the binding region of the peptide. Peptides were developed in different ways, for example for targeted transport using carrier peptides for tumor and tissue targeting [34,35].

The systemic side effects of therapeutic agents on healthy and non-targeted tissues are one of the most serious problems particularly in oncology and gene therapy. Many of the existing pharmaceutics have their limitations due to the lack of selective delivery into their target tissues. Consequently, site/organ-specific drug targeting is an attractive strategy to reduce unwanted side effects and to enhance drug efficacy within the targeted tissue [36,37]. Here we focus on kidney targeting with a collection of reviews and perspectives that highlights some of the main strategies in this field.

Discussion

Kidney-specific drug delivery

The major functions of the kidney are the maintenance of body water and sodium balance, the filtration of waste products from the bloodstream, the secretion of hormones, and multiple homeostatic controls such as the acid-base regulation of the blood. The current number of 280 million patients suffering from chronic kidney diseases (CKD) increases incessantly. The costs for the treatment of kidney diseases are predicted to exceed 1 trillion US$ over the next decade. Drugs for treating kidney diseases are often limited by tolerability and extra-kidney safety concerns, which prevent their use at maximally effective doses. Targeting

drugs to the kidneys may circumvent these limitations and reduce toxicity of new, established, and pre-existing drugs. It has therefore evolved as a cherished but elusive goal in pharmaceutical sciences. For examples, long-term therapy of CKD is accompanied by serious side effects and numerous promising drug candidates failed during clinical trials due to safety issues and lack of efficacy, e.g., bardoxolone methyl and paricalcitol in CKD, avosentan in diabetic nephropathy,and sirolimus and everolimus in autosomal dominant polycystic kidney disease (ADPKD) [38]. Covalently linked drug-polymers can be applied to improve the therapeutic index of toxic drugs. To prevent the shift in cytotoxicity pattern resulting from the delivery system, biodegradable delivery systems such as peptide-based carriers were preferred [39]. Another approach makes use of some endogenous enzymes having relatively high concentrations in kidneys such as amino acid L-decarboxylase and γ-glutamyl transpeptidase [40]. Based on this, substrates of these enzymes to chemically modify drugs had been prepared and used in the hope that drug would be released in proximal tubular cells via the relevant enzyme.

Consequently, efforts have been made to enable a specific uptake of drugs in the kidneys [40]. Attempts to use small protein carriers such as lysozymes were hampered by their renal toxicity and cardiovascular side effects [41]. Prodrugs that are activated by kidney-associated enzymes showed low accumulation rates in the kidneys [42]. Streptavidin conjugates that target the high levels of endogenous biotin in the kidneys failed due to unfavourable pharmacokinetics of this high molecular weight protein [43]. Liposomal formulations [44], dendrimer conjugates [21] as well as copolymer conjugates [45] also did not yet exert the properties required. Relatively few papers on drug delivery or targeting research however appear in the top ranking scientific journals, probably because the concepts or technologies presented are often not recognized as most innovative scientifically but rather application oriented [46].

The majority of kidney-specific delivery systems target the proximal tubular cells and may contribute in the treatment of renal diseases such as kidney transplantation, ureteral obstruction, diabetes, proteinuria, and in some diseases involving changes in renal tubular function such as Fanconi and Bartter´s syndrome.

Alkylglycoside and sugar-modified low-molecular-weight peptides: Alkylglycoside and sugar-modified low-molecular-weight peptides have been shown to have renal targeting potential *in vivo*. In 1999, Suzuki et al. [47] had suggested a novel transport mechanism in the kidneys that can be used for the specific renal delivery of glycosylated peptides [47]. Their observations reveal the saturation of the renal uptake *in vivo* with increasing dose, and there is an effective mechanism for uptake from blood. Moreover, they had proposed that the renal uptake may not be dependent on derivatives having a cationic nature. However, Shirota et al. [48] had suggested that the anionic moiety could reduce the renal targeting efficiency [48]. Thus, the targeting efficacy of the alkylglucoside vector seems to depend on, at least, the size and charge of the ligand that it delivers.

Low molecular weight proteins (LMWPs)

LMWPs involve active proteins in the circulatory system such as enzymes (lysozymes), immune proteins (such as light chain immunoglobulins) and peptide hormones (such as insulin). However, lysozyme represents the most widely studied LMWP. The most extensively studied kidney-targeted lysozyme-conjugates are with naproxen (peptide bond) [49-51], triptolide (ester linkage) [52,53], captopril (disulfide bond) [54-57], and anticancer agents [1,58]. Moreover, a number of other drugs have been linked to lysozyme or various carriers in several ways [59,60].

LMWPs can be filtered at the glomerulus and reabsorbed in the renal tubules. Generally, the kinetics of the macromolecular carrier over rule the intrinsic kinetics of the drug. Therefore, a drug-macromolecular carrier conjugate is rapidly cleared from the blood supply and undergoes drug release and activation in lysosomes. Normally, distribution of the released drug in the kidney is relatively slow allowing more concentration of drug in the kidneys relative to plasma [61-64]. However, due to the diversity and variety of the functional groups presented on the LMWP, conjugation procedures should be performed carefully to avoid the very common self-aggregation and degeneration. Additionally, attempts to use LMWPs such as lysozymes were hampered by their renal toxicity and cardiovascular side effects [41].

Low molecular weight chitosan (LMWC)

Chitosan has been widely used in drug delivery systems due to its excellent biocompatibility and biodegradability. It is derived from chitin and consists of glucosamine and *N*-acetyl-glucosamine. However, different degrees of acetylation and molecular weights of LMWC had been investigated for their kidney-specific drug delivery [65,66]. LMWC is specifically taken up by renal tubular cells probably via megalin [67-69]. However, LMWC was cleared from the kidneys more rapidly in comparison with lysozyme, therefore, it has safer pharmacokinetic profile.

Chitosan oligomers can be a potential drug carrier for renal targeting delivery. It was used as a carrier for zidovudine (AZT), since the later has a very short half-life and is eliminated very quickly in human plasma and kidney after administration [70]. However, more characterization and investigation worth to be performed.

Anionized polyvinylpyrrolidone (PVP) and Poly(vinylpyrrolidone-co-dimethyl maleic acid) (PVD):

PVD had been reported as a carrier for kidney-specific drug delivery. However, the polymer needs long time (24h) after i.v. injection in order to accumulate only 80% specifically in the kidneys. Further study in mice demonstrates that there is a relationship between the molecular weight and the charge of PVD derivatives regarding their renal accumulations. Additionally, carboxylated PVP was taken up by the renal proximal tubular epithelial cells *in vivo* after i.v. injection [71,72].

G3-C12 peptide: The galectin-3 carbohydrate recognition domain (G3-C12) was shown to specifically accumulate in mouse kidneys after i.v. injection [73]. The peptide-captopril conjugate was evaluated with a disulfide bond which can be cleaved by reduced glutathione in the kidney. The peptide–drug conjugate accumulated specifically in the kidney soon after i.v. injection into mice, and the accumulation had been attributed largely to the reabsorption of the peptide by the renal proximal tubule cells [74].

Epsilon Poly-L-lysine-Derivatives (εPLL) and The Carrier Peptide $(KKEEE)_3K$: Recently, Mier and co-workers had started a development program for a kidney-specific carrier peptide. [75] Based on the effect of lysine which interacts with receptors on the apical side of proximal tubule cells [76,77], DOTA-εPLL showed very exclusive accumulation in the kidneys. Due to the structure of DOTA-εPLL comprising unnatural peptide bonds, DOTA as an additional compound, and a long retention in the kidneys, a peptide consisting only of natural amino acids and standard peptide linkages was developed. Based on their findings, the authors stated that a balanced ratio between positively and negatively charged functional groups is obviously essential to achieve high kidney specificity. Different peptides were synthesized to identify a carrier with improved clearance properties and balanced ratio between positive and negative charged functional groups. The ideal peptide not containing any unnatural residues was found to be $(KKEEE)_3K$ [75]. The results obtained demonstrate an indication of megalin-mediated endocytosis of $(KKEEE)_3K$ into proximal tubule cells. The carrier peptide $(KKEEE)_3K$ can circumvent the specific disadvantages of LMWP and other macromolecular carriers. It shows high kidney selectivity, even with conjugated drugs (e.g. ciprofloxacin), rapid kidney accumulation, renal clearance within a few hours, and has a nontoxic profile. Therefore, $(KKEEE)_3K$ is a promising carrier for renal targeting.

Particulate kidney-targeted drug delivery systems: Usually, particulate drug delivery systems such as nanoparticles or liposomes have been omitted in renal targeting due to their large size and the limitation of glomerular filtration. They are being investigated for numerous medical applications and are showing potential as an emerging class of carriers for drug delivery. Despite proven success in their accumulation at a selected few organs such as tumor and liver, reports on their effective delivery to other organs still remain scarce. Choi et al. [78] showed that PEGylated gold nanoparticlesof ~75 ± 25-nm diameters target the mesangium of the kidney demonstrating the effects of particle diameter on targeting the mesangium [78]. This finding establishes design criteria for constructing nanoparticle-based delivery systems for targeting diseases that involve the mesangium. Moreover, this finding is of special interest since the majority of kidney-specific drug delivery systems are targeting the proximal tubular cells rather than the mesangium. On the other hand, Tuffin et al. [79] had targeted the mesangium by preparing liposomes with $F_{ab'}$ fragments of OX7 mAb (OX7-IL) [79]. However, rats that were given a single intravenous injection of low-dose doxorubicin encapsulated in OX7-IL showed extensive glomerular damage.

Conclusion

Kidney diseases require, usually, long-term administration of therapeutics; therefore, they are always accompanied with systemic toxicities and adverse side effects. Consequently, it is necessary to develop a kidney-targeted drug delivery system in order to overcome these obstacles .Several attempts have been performed aiming to target the kidneys, and the majority of kidney-specific delivery systems targets the proximal tubular cells and may contribute to the treatment of renal diseases. Such strategies involve LMWPs, PVP, PVD, LMWC, G3-C12 peptide, εPLL derivatives and the carrier peptide $(KKEEE)_3K$. The specific uptake by renal proximal tubular cells is confirmed in many cases to bemegalin-mediated endocytosis. Additionally, the overall charge of the carrier seems to play a key role in kidney-specific drug delivery. On the other hand, particulate drug delivery systems such as nanoparticles or liposomes seem to be useful in targeting diseases that involve the mesangium. However, the particle diameter is crucial for targeting the mesangium. Finally, the challenge remains in translating the use of those carriers in clinical trials and applications.

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