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Retrometabolic drug design: Principles and recent developments*

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Abstract: Retrometabolic drug design incorporates two major systematic approaches: the design of soft drugs (SDs) and of chemical delivery systems (CDSs). Both aim to design new, safe drugs with an improved therapeutic index by integrating structure–activity and –metabolism relationships; however, they achieve it by different means: whereas SDs are new, active therapeutic agents that undergo predictable metabolism to inactive metabolites after exerting their desired therapeutic effect, CDSs are biologically inert molecules that provide enhanced and targeted delivery of an active drug to a particular organ or site through a designed sequential metabolism that involves several steps. General principles and recent developments are briefly reviewed with various illustrative examples from different therapeutic areas with special focus on soft corticosteroids and on brain targeting.

Keywords: drug design; metabolism; brain targeting; hydrolysis; oxime.

INTRODUCTION

Despite major advancement in the elucidation of the molecular/biochemical mechanisms of drug actions and in our abilities to screen compounds and identify highly active hits, there was no corresponding increase in launched new chemical entities (NCEs) approved by regulatory agencies. This is most likely due to our limited understanding as to what makes ultimately a good drug as well as to increasing difficulties caused by the existing stringent regulations. The problem is also highlighted by the fact that most relatively recently launched drugs were not only derived by modifications of known drug structures or published lead structures, but were even closely related to their original leads, and new technologies such as combinatorial chemistry or high-throughput screening (HTS) still had no significant impact [1]. Hence, it is still true to a surprising degree that "the most fruitful basis for the discovery of a new drug is to start with an old drug" as advised by Sir James Black [2,3]. Retrometabolic drug design approaches provide general drug design strategies very much along these lines as they usually start from a known lead structure and focus on designing safer, less toxic, and intrinsically better-targeted drugs either through a soft drug (SD) or chemical delivery system (CDS) designs.

It is important to note that the drug design process should not be focused solely on increasing activity, but rather on increasing the therapeutic index, which is a reflection of the degree of selectivity or margin of safety (usually defined as the ratio between the median toxic and the median effective dose, $TI = TD_{50}/ED_{50}$). It is also important to take into account the possible metabolic conversion of the drug

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(D) because it can generate various metabolites including, for example, analog metabolites (D_1, D_2, …), which have structures and activities similar to the original drug but have different pharmacokinetic properties, other metabolites (M_1, M_2, …) including inactive ones (M_i), and potential reactive intermediates (I^*_1, I^*_2, …), which can create various kinds of cell damage by forming toxic species (Fig. 1). All these compounds are present simultaneously and at varying concentrations as they tend to have different pharmacokinetic profiles; hence, the observed total activity and toxicity are a combination of the intrinsic activities and toxicities of the original drug and all these various metabolic products.

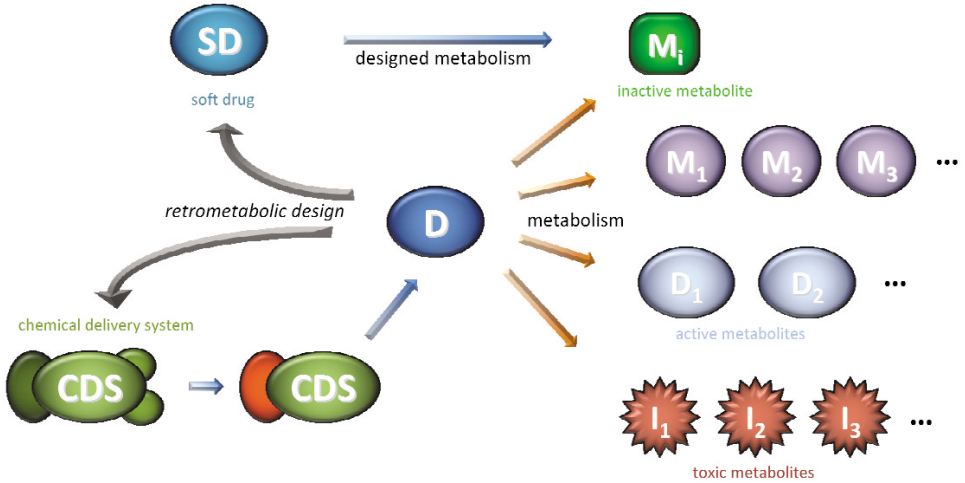

Fig. 1 Schematic representation of retrometabolic drug design approaches, including SD and CDS designs and their integration with the general metabolic pathways of drugs (D).

RETROMETABOLIC DRUG DESIGN

These drug design approaches were designated as *retrometabolic* to emphasize the fact that metabolic pathways are designed going backwards compared to actual metabolic processes (Fig. 1) in a manner somewhat similar to E. J. Corey's *retrosynthetic* analysis, in which synthetic pathways are designed going backwards compared to actual synthetic laboratory operations. They represent systematic methodologies that fully integrate structure–activity and –metabolism relationships into the design process to obtain targeted, safe, locally active compounds with an improved therapeutic index and include two distinct approaches: the design of SDs and of CDSs [4–7]. *SDs* are new, active therapeutic agents, often isosteric–isoelectronic analogs of a lead compound, with a chemical structure specifically designed to allow predictable metabolism into inactive metabolites after exerting the desired therapeutic effect. *CDS*s are biologically inert molecules that require several steps to convert to the active drug and that enhance drug delivery to a particular organ or site. As schematically illustrated in Fig. 1, both rely on enzymatic reactions; however, whereas a CDS is inactive as administered and sequential enzymatic reactions provide the differential distribution and ultimately release the active drug, SDs are active as administered and are designed to be easily metabolized into inactive species. Assuming ideal circumstances, with a CDS, the drug should be present at the target site and nowhere else in the body because enzymatic processes produce the drug only at this site, whereas with an SD, the drug should be present at the site and nowhere else in the body because enzymatic processes destroy the drug at those sites. Figures 2 and 3 provide specific examples for the schematics of Fig. 1 using as leads estradiol (Fig. 2, SD and brain-targeting CDS design) and metoprolol (Fig. 3, SD and ocular-targeting CDS design), respectively; corresponding details are discussed in the following sections.

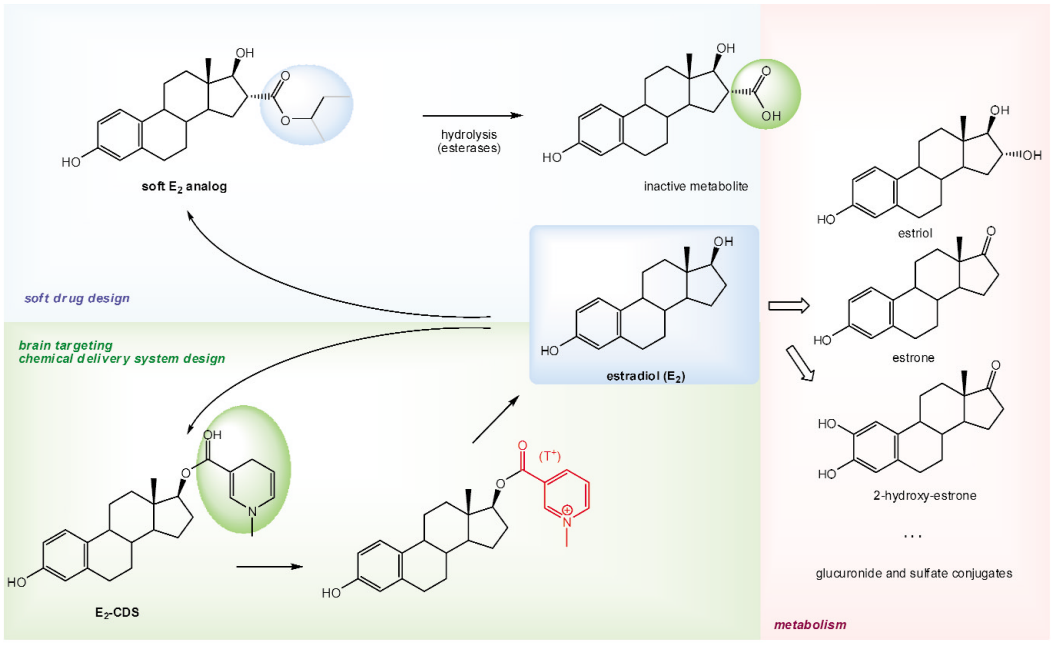

Fig. 2 Illustration of retrometabolic approaches together with metabolic pathways for estradiol (E_2), which has been used for both brain-targeting CDS (bottom left) and SD design (top left).

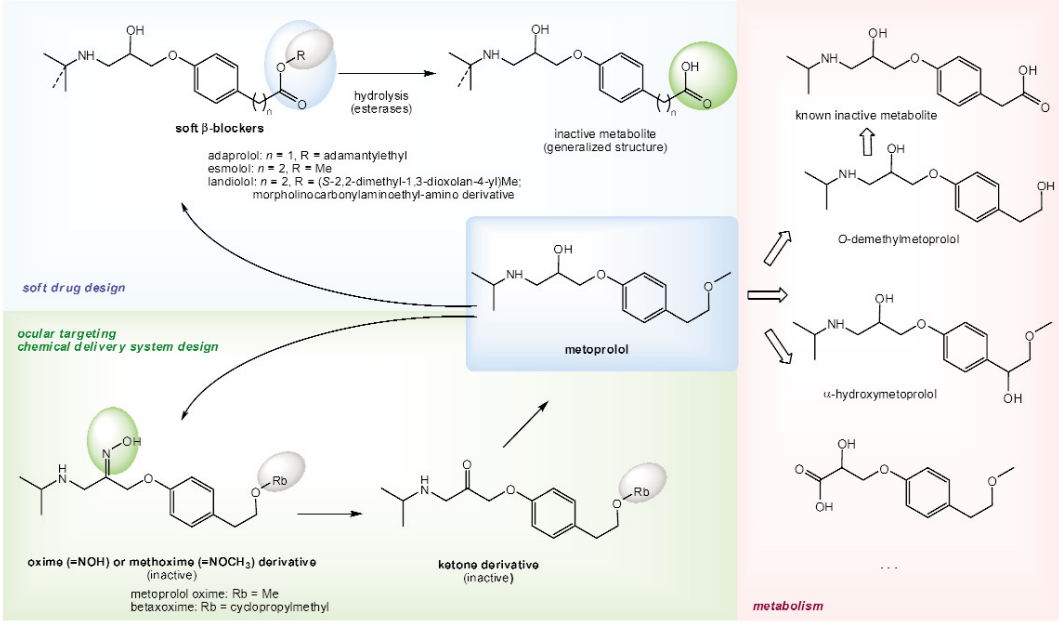

Fig. 3 Illustration of retrometabolic approaches together with metabolic pathways for β-blockers, which has been used for both ocular-targeting CDS (bottom left) and SD design (top left) using metoprolol as a representative lead.

SOFT DRUG DESIGN

By definition, SDs are newly designed, therapeutically active compounds (most often close structural analogs of a known lead compound) specifically designed to allow predictable metabolism into inactive metabolites after exerting the desired therapeutic effect [8–12]. Hence, they produce targeted, localized pharmacological activity, but no undesired systemic activity or toxicity as they are promptly deactivated when they distribute away from this site. The goal is not to avoid metabolism, but rather to control and direct it in order to avoid the formation of toxic or active metabolic products. For this reason, SDs should preferably rely on inactivation by hydrolytic enzymes that are ubiquitously distributed and can carry out the desired rapid metabolism extrahepatically and more reliably than oxygenases, which are mostly located in the liver and are subject to saturation, inhibition, and induction. *Prodrugs* are often confused with SDs mainly because both are specifically designed to undergo predictable metabolic changes and both mostly rely on enzymatic hydrolysis for these metabolic changes [13]. However, this designed-in change is activation for prodrugs and deactivation for SDs.

SD approaches can be classified into five subclasses: (1) inactive metabolite-based SDs, (2) soft analogs, (3) active metabolite-based SDs, (4) activated SDs, and (5) pro-SDs. However, of these approaches, the first two have proven to be the most useful and successful strategies, and have been applied the most frequently. *Inactive metabolite-based SDs* are active compounds designed starting from a known inactive metabolite of an existing drug. Sometimes, not an actually observed, but an assumed (i.e., hypothetical) inactive metabolite can also be used as a starting point. This is then converted into a steric and electronic analog of the original drug that is active, but allows facile, single-step metabolism back to the very inactive metabolite the design started from. *Soft analog* SDs are close structural analogs of known active drugs that have a specific metabolically sensitive moiety built into their structure to allow a facile single-step deactivation after the desired therapeutic role has been achieved. The two approaches overlap somewhat, and certain SDs can be considered as resulting from either of them.

Soft drug examples

The SD concept was introduced during the 1970s [8], and since then it has been applied in a large number of therapeutic areas. Detailed comprehensive reviews of all major aspects have been published [7,12]. Our laboratory mainly focused on the design of soft corticosteroids (e.g., loteprednol etabonate, etiprednol dicloacetate) [14], soft β-blockers (e.g., adaprolol) [15], and soft anticholinergics (e.g., tematropium) [16]. For soft corticosteroids and soft anticholinergics, enough and sufficiently varied novel structures have been generated by now to allow the development of detailed quantitative structure–activity relationships (QSARs) [17–19] by taking into account size-related effects through a bilinear LinBiExp model [20,21]. A number of SD approaches both by our laboratories and by many others already resulted in marketed drugs such as loteprednol etabonate (LE), a soft glucocorticoid, esmolol and landiolol, soft β-blockers, or remifentanil, a soft opiod analgetic (Fig. 4). Some therapeutic compounds can also be considered as "accidental" SDs, i.e., drugs that are, in fact, SDs even though they were not intentionally designed as such. For example, methylphenidate, a methyl ester-containing piperidine derivative that is structurally related to amphetamine and is now widely used for the treatment of attention deficit hyperactivity disorder (ADHD). Because methylphenidate is rapidly hydrolyzed [22] into an inactive [23], acidic metabolite (ritalinic acid), it can be considered a SD, and this is certainly a main reason behind its relative safety that makes possible its widespread pediatric use. Some endogenous compounds, such as steroid hormones or neurotransmitters (like dopamine, GABA, and others) can be considered as natural SDs because there are efficient, fast metabolic ways for their disposition without going through highly reactive intermediates.

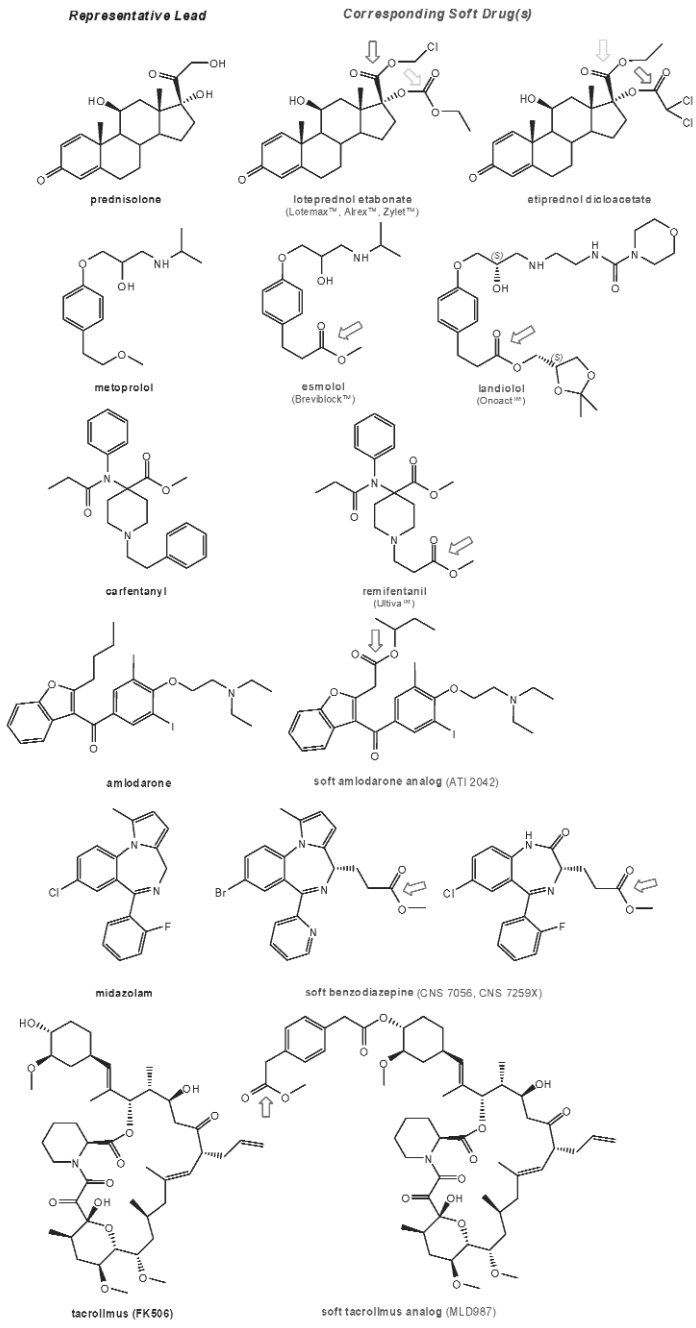

Fig. 4 Selected SDs together with their corresponding lead structures and site of designed-in hydrolytic inactivation (denoted by arrows).

SD design approaches are increasingly widely applied both in industrial and academic settings; some of the more interesting recent developments include, for example:

- soft estradiol analogs developed by Labaree and coworkers at Yale University (Fig. 2) [24,25],
- soft amiodarone analogs (e.g., ATI-2042) [26,27]) and soft cisapride analogs (ATI-7505) [28] developed at Aryx Therapeutics,
- soft cyclosporin A analogs explored at Enanta [29],
- soft tacrolimus analogs (e.g., MLD987) investigated at Novartis (Fig. 4) [30],
- novel soft cytokine inhibitors developed at Janssen [31],
- soft benzodiazepine analogs (CNS7259X, CNS7056) that are midazolam/bromazepam analogs originally developed at GlaxoSmithKline on the basis of the remifentanil experience (Fig. 4) [32–35],
- intended soft mometasone furoate analogs investigated at Novartis [36],
- soft 16-en-22-oxa-vitamin D_3 analogs explored at Chugai [37,38],
- soft biphenylic cannabinoids investigated by Minutolo and coworkers at the University of Pisa [39], and many others.

Soft corticosteroids

The field of anti-inflammatory corticosteroids provides one of the most successful fields for SD design. Traditional corticosteroids are very useful drugs because of their ability to exert intense biological effects in almost any organ, but, for the same reason, they also tend to have multiple adverse effects that seriously limit their usefulness. Not surprisingly, the glucocorticoid receptor represents the target with the most number of approved drugs (together with the histamine H_1 receptor) [2]. Systemic side effects tend to be dose-dependent and typically include, for example, weight gain, fat redistribution, insulin resistance, myopathy, osteoporosis, hypertension, increased IOP, growth inhibition, and others [40–43]. Corticosteroids also tend to form various steroidal metabolites, and their presence can lead to undesirably complex situations. Hence, SD approaches are particularly well suited for this area especially for the design of novel inhaled, intranasal, or topically applied corticosteroids. However, to successfully separate the desired local activity from systemic toxicity, it is important to reach an adequate balance between activity/distribution and rate of metabolic deactivation. By focusing exclusively on too fast metabolic degradation, activity could also be lost—a likely reason for the failure of some soft steroid approaches.

We followed a classic inactive metabolite-based SD approach with cortienic acid, a known inactive metabolite of hydrocortisone [44], as lead. Starting from this structure, more than 120 first-generation soft steroids have been synthesized by modifications of the 17β ester function and the 17α hydroxy function, together with other changes (introduction of $\Delta^{1,2}$, fluorination at 6α and/or 9α, methylation at 16α or 16β). From these, *loteprednol etabonate* (Fig. 4) has been selected for clinical development on the basis of various considerations including therapeutic index, synthetic availability, and "softness" (the rate and easiness of metabolic deactivation). Animal studies proved that, consistent with its design, LE is indeed active, it is metabolized into its predicted metabolites, and these metabolites are inactive. Following the requisite preclinical and toxicology studies, clinical studies provided evidence that LE is a safe and effective treatment for contact lens-associated GPC, seasonal allergic conjunctivitis, post-operative inflammation, or uveitis [45,46], and it is now the active ingredient of three FDA-approved ophthalmic preparations. A retrospective study showed that even long-term (>12 months) use of LE caused no reported adverse effects [47]. Currently, LE is also being developed for treatment of asthma, rhinitis, colitis, and dermatological problems [14].

More recently, we also focused on a new class of soft steroids with a unique design having 17α-dichloroester substituents [48], and selected *etiprednol dicloacetate* (ED, Fig. 4) for development. No known corticosteroids contain halogen substituents at this 17α position; nevertheless, the pharmacophore portions of these second-generation soft steroids, including the halogen atoms at 17α, can be positioned so as to provide excellent overlap with those of the traditional corticosteroids [17]. Contrary to

the first generation of soft steroids including LE, in these soft steroids, hydrolysis primarily cleaves not the 17β-positioned, but the 17α-positioned ester (Fig. 4). Nevertheless, the corresponding metabolites are also inactive. ED was shown to be as, or even more effective, than budesonide in various asthma models, and, in agreement with its soft nature, it was found to have low toxicity in animal models and in human clinical trials [14,49–51].

Computer-aided soft drug design

The number of possible SD alternatives that can be designed for a given lead depends on its chemical structure, but in certain cases it can be a considerable number. In such cases, it may be tedious and difficult to find the best SD candidate by simple trial and error procedures. Therefore, computer-aided design can be particularly useful here: by introducing quantitative measures through the calculation of various molecular properties, including hydrolytic lability [52,53], and by generating an estimated ranking order on the basis of the steric and electronic analogy compared to the original lead, it can provide an analogy-based ranking order, and it can help in eliminating candidates that are unlikely to achieve reasonable activity ahead of their synthesis and experimental testing [7,12,54,55]. This can now be done by a fully computerized expert system that combines the various structure-generating rules of SD design with these predictive quantitative structure–activity/structure–metabolism relationship (QSAR/QSMR) models and can generate virtual libraries of new SD structures of interest as well as assist in selecting the most promising new candidates; detailed reviews have been published [55–57].

CHEMICAL DELIVERY SYSTEMS

On the other side of retrometabolic design (Fig. 1), CDS approaches provide novel, systematic methodologies for targeting active biological molecules to specific target sites or organs based on predictable, multistep enzymatic activation [6,58,59]. The bioremovable moieties attached to the drug that is the subject of targeted delivery include a *targetor* (T) moiety, which has to achieve the site-specific targeting, and (optional) *modifier functions* ($F_1...F_n$), which serve as lipophilizers, protect certain functions, or fine-tune the necessary molecular properties to prevent premature, unwanted metabolic conversions.

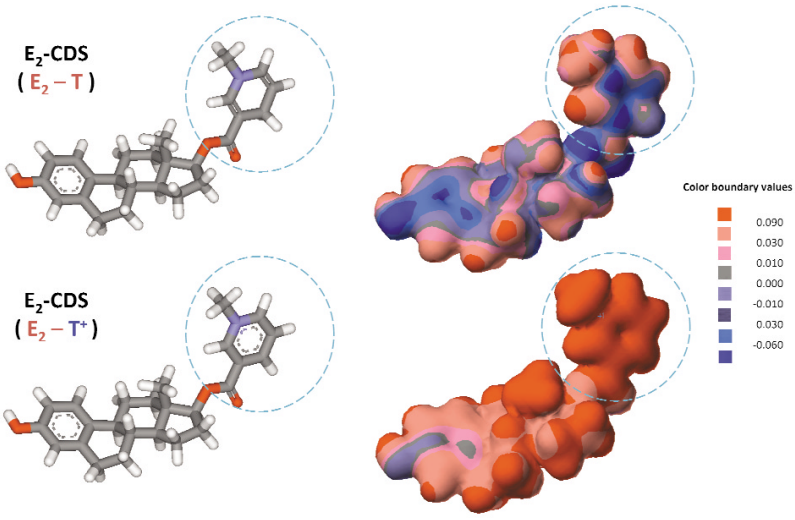

Fig. 5 Comparison of the 3D structures and electron distributions of the brain-targeting E_2-CDS in its administered, neutral form (E_2-T, top) and metabolically generated, quaternary form (E_2-T^+ bottom).

The two main classes are represented by the enzymatic physicochemical-based CDSs, which exploit site-specific traffic properties by sequential metabolic conversions that result in considerably altered transport properties and are used for brain targeting, and by site-specific enzyme-activated CDSs, which exploit specific enzymes found primarily, exclusively, or at higher activity at the site of action and are used for ocular targeting.

Brain-targeting CDSs

Design principles

Because the blood–brain barrier (BBB) tightly segregates the brain from the circulating blood [60–62], many therapeutic agents cannot be effectively delivered and/or sustained within the brain and, therefore, are ineffective in the treatment of cerebral or central nervous system (CNS)-related diseases. Capillaries of the vertebrate brain and spinal cord are lined with a layer of special endothelial cells that lack fenestrations and are sealed with tight junctions forming what is known as BBB. Consequently, only lipid-soluble solutes that can freely diffuse through the capillary endothelial membrane may passively cross the BBB, and lipophilicity (as measured, for example, by the log octanol/water partition coefficient, log $P_{o/w}$) is a good predictor of BBB permeability [63,64]. Essentially, all drugs currently used for brain- or CNS-related disorders are lipid-soluble compounds that can readily cross the BBB following their administration, and various strategies are being continuously explored to overcome these problems and to achieve brain delivery or if possible brain-targeted delivery for other therapeutic agents [65]. Among existing brain-targeted drug delivery approaches, CDSs are the only one attempting not only to increase influx, but also to decrease efflux through the BBB.

Brain-targeting redox-type CDSs can be used not only to deliver compounds that otherwise have no access to the brain, but also to target and retain compounds within the brain by using a multistep sequential metabolism approach. These CDSs are obtained by chemically attaching a T moiety to the original drug structure and, if needed, some additional modifier/protective functions. Upon administration, the resulting CDS is distributed throughout the body. Predictable enzymatic reactions convert the original CDS by removing some of the protective functions and modifying the T moiety, leading to a precursor form (T^+–D), which is still inactive, but has significantly different physicochemical properties (Fig. 5). While the charged T^+–D form is locked behind the BBB into the brain, it is easily eliminated from the body due to the acquired positive charge, which enhances water solubility. After some time, the delivered drug (D) (as the inactive, locked-in T^+–D) is present essentially only in the brain, and carboxylic esterases–mediated hydrolysis of this intermediary form provides sustained and brain-specific release of the active drug. As a result of this process, the system not only achieves delivery to the brain, but it provides preferential delivery, i.e., brain targeting, making possible smaller doses and reduced peripheral side effects. Furthermore, because of the "lock-in" mechanism, it also provides more prolonged effects. The CDS concept evolved from the prodrug concept, but became essentially differentiated by the introduction of T moieties, which are responsible for targeting, site-specificity, and lock-in, and by the employment of multistep activation [58].

In principle, many T moieties are possible for a general system of this kind, but the one based on the 1,4-dihydrotrigonelline ↔ trigonelline (coffearine) system, where the lipophilic 1,4-dihydro form (T) is converted in vivo into the hydrophilic quaternary form (T^+), proved the most useful (Fig. 2). This conversion takes place easily everywhere in the body since it is closely related to that of the ubiquitous NAD(P)H ↔ $NAD(P)^+$ coenzyme system. The CDS approach has been explored with a wide variety of drug classes; detailed reviews have been published before [7,59]. Area-under-the-curve (AUC)-based *site-targeting indexes*, STI = AUC_{target}/AUC_{blood}, provide pharmacokinetically accurate quantitative measures of the effectiveness of delivery to the intended site of action, and *targeting enhancement factors*, TEF = $STI^{Delivery\ System}/STI^{Drug\ Alone}$, measure the relative improvement in the STI produced by

administration of the delivery system compared to administration of the drug itself [7,65]. In a number of cases, they clearly showed that CDSs can produce substantial increase of the targeting effectiveness, often more than an order of magnitude; detailed reviews have been published [7,59,66].

Estradiol-CDS (E_2-CDS)

Among CDS approaches explored to date, estradiol CDS (E_2-CDS) is in the most advanced investigation stage: it has recently completed phase I/II investigation with a new buccal formulation [67]. Estradiol (E_2) is the most potent human estrogen, and because many of its pharmacological effects are CNS-mediated, there are several potential therapeutic applications for a brain-targeted delivery system including the treatment of menopausal vasomotor symptoms ("hot flashes"), the treatment and/or prevention of various types of dementia including Alzheimer's disease, male or female sexual dysfunction, and possibly neuroprotection. Originally, a number of molecular manipulations have been explored for this CDS, and the efficacy of 3-substituted vs. 17-substituted [68] or the efficacy of different *N*-substituted T moieties (*R* methyl to hexyl or benzyl) [69] have been evaluated. However, the, 17-(1,4-dihydrotrigonelline)-substituted E_2-CDS shown in Fig. 2 is the compound of choice. Various animal studies demonstrated effective brain targeting and confirmed the long-lasting pharmacological activity (Fig. 6) [67,70,71].

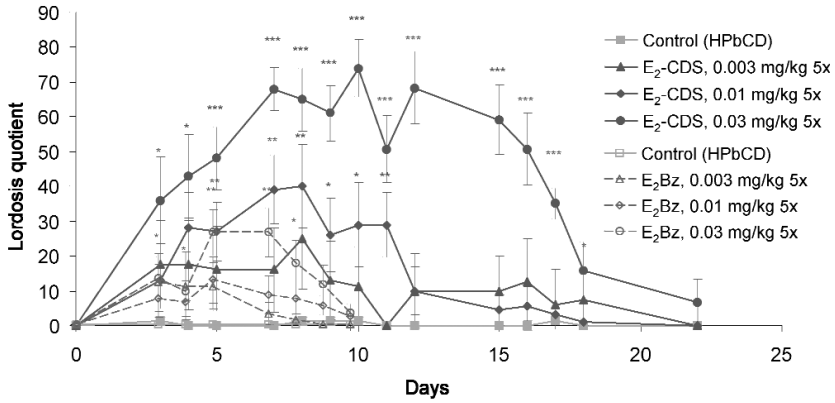

Fig. 6 Effect of different doses of E_2-CDS compared to those of the isolipophilic E_2-benzoate (E_2Bz) on the lordosis behavior of castrated female rats [71]. Lordosis quotient calculated as 100 × number of lordosis/10 mounts. Data are mean ±SE for 8–12 animals per group. E_2-CDS was administered for 5 days i.v. dissolved in 27 % HPβCD solution. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ using Mann–Whitney U test.

Unfortunately, the same physicochemical characteristics that allow for successful delivery somewhat also complicate the development of acceptable pharmaceutical formulations. The increased lipophilicity, which is needed for BBB permeability, also confers poor aqueous solubility. The oxidative lability, which is needed for the "lock-in" mechanism, and the hydrolytic instability, which releases the modifier functions or the active drug, combine to limit the shelf-life of the CDS. However, the use of cyclodextrins can provide acceptable solutions as they can increase both aqueous solubility and stability [72], and cyclodextrin-based formulation already made it possible, for example, for E_2-CDS to reach human phase I/II clinical trials [67,70].

Molecular packaging

The CDS approach has also been extended to achieve successful brain deliveries of neuropeptides such as Leu-enkephalin, thyrotropin-releasing hormone (TRH), and kyotorphin analogs [7,59,73–75]. Brain delivery of peptides is particularly difficult because of their rapid metabolic degradation by peptidases and their often unfavorable lipophilicity profile. Therefore, the successful brain delivery of peptides re-

quires three issues to be solved simultaneously: (1) enhance passive transport by increasing the lipophilicity, (2) ensure enzymatic stability to prevent premature degradation, and (3) exploit the lock-in mechanism to provide targeting. This has been achieved with a complex *molecular packaging* strategy, in which the peptide unit is part of a bulky molecule dominated by lipophilic modifying groups (L) that direct BBB penetration and prevent recognition by peptidases (Fig. 7). The efficacy of the CDS package was strongly influenced by modifications of the spacer (S) moiety, which consisted of strategically used amino acids that ensured the timely removal of the charged T from the peptide, and the lipophilic (L) moiety. The bulkier cholesteryl group used as L showed a better efficacy than the smaller adamantaneethyl, but the spacer (S) function turned out to be most important factor for manipulating

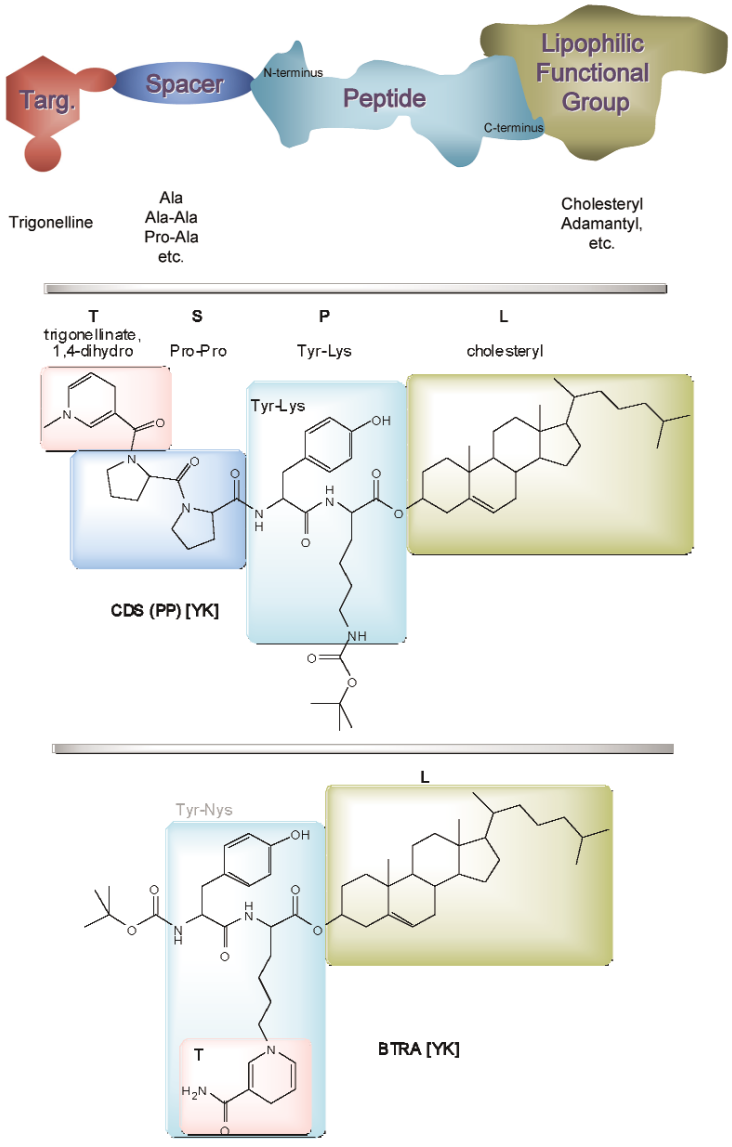

Fig. 7 Schematic illustration of the molecular packaging approach used for brain-targeted delivery of neuropeptides (top) and corresponding structures for the CDS and BTRA of the kyotorphin analog Tyr-Lys (YK).

the rate of peptide release and pharmacological activity: proline, proline-proline, or proline-alanine spacers produced the best in vivo pharmacological effects. *Brain-targeting redox analogs* (BTRAs), in which the T moiety is not attached to the peptide from outside, but is integrated within novel *redox* amino acids building blocks that replace the original basic amino acid of the active peptide (Fig. 7), have also been explored for kyotorphin and its analogs [74] as well as for TRH in a copycat design [76].

Ocular-targeting CDSs

These CDSs exploit enzymatic conversions that take place primarily, exclusively, or at higher activity at the site of action as a result of differential distribution of certain enzymes. For example, successful site- and stereospecific delivery of intraocular pressure (IOP)-reducing β-adrenergic blocking agents to the eye was achieved with a retrometabolic design [15,77–79]. The resulting compounds contained a β-amino oxime or alkyloxime function that replaced the corresponding β-amino alcohol pharmacophore part of the original molecules (Fig. 3, bottom part). They are enzymatically hydrolyzed within the eye by enzymes located in the iris-ciliary body, and subsequently reductive enzymes also located in the iris-ciliary body produce only the active *S*-(–) stereoisomer of the corresponding β-blockers [80].

The oxime or methoxime derivatives exist in alternative *Z* (syn) or *E* (anti) configuration. Whereas *Z*/*E* isomerization in buffers is usually relatively slow, it is much faster in biological fluids indicating enzymatic involvement (e.g., isomerization is 300–500 times faster in biological fluids than in simple buffer for betaxolone oxime and methoxime [81]). Several of these oxime and alkyloxime derivatives showed significant IOP-lowering activity, but their systemic (i.v.) administration did not produce the active β-blockers metabolically; therefore, they were void of any cardiovascular activity, a major drawback of classical antiglaucoma agents. Alprenoxime and betaxoxime, the oxime derivatives of alprenolol and betaxolol, respectively, have also entered the clinical investigation phase; for a detailed recent review, see [15].

CONCLUSION

In conclusion, retrometabolic approaches incorporate two drug design approaches to obtain SDs and CDSs, respectively. SDs and CDSs achieve their drug-targeting roles in opposite ways, but they both rely on designed metabolism to control drug distribution and action and to increase safety. These approaches are general in nature, and the corresponding specific design principles can be applied to essentially all drug classes. Because they usually start with a known active lead in a selected therapeutic area, they are more likely to result in an approvable drug product than most other drug design approaches, and, in many cases, even dedicated computer programs are available to enhance their application.

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