2. Brain-Specific Drug Delivery

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Targeted drug delivery is one of the most important goals of pharmaceutical research and development. Physical, biological, or molecular systems which act to concentrate a pharmacologically active agent at its pathophysiologically relevent site would provide significant advantages over conventional drugs. If successful, in this way a greater portion of the administered dose of a drug is sequestered at a particular locus, the delivery system should be highly efficacious, and the drug dose could be reduced. In addition, toxicities related to nontarget tissues and sites would be significantly attenuated, since lower concentrations of the pharmacologically active agent are present. Ultimately, lowering the effective dose and increasing the dose of a drug required to initiate toxicity results in a significant improvement in the therapeutic index (TI). This parameter, representing the ratio between toxic and effective dose, is arguably the most important property of a drug which must be optimized during the drug design, development, and testing process.

Since the development of the receptor theory, attempts have been directed toward developing new therapeutic agents that would have a singular target, that is, would be bound only to one kind of receptor. It was hoped in this way that aberrant toxicity would be avoided and only the desired therapeutic gain would be produced. Of course, this concept would work very well if diseases would have their own specific receptors which would allow this individual design to affect only the specific disease. Unfortunately, the situation is not that simple. Most receptors are generally distributed throughout the body, while various diseases many times are localized. What this means is that even finding a drug which binds to one specific receptor type, and as desired would produce agonistic or antagonistic activity, the therapeutic index may still not be too favorable. Recognizing this fact led to the idea that something additional had to be done to enhance the therapeutic index and that is to localize the drugs at the desired site of action, beyond receptor targeting. This lesson was also learned from nature. It is well known that neurotransmitters like dopamine are released at specific parts of the brain producing the desired action, but they are also localized within the brain by the blood-brain barrier (BBB), which is virtually impenetrable to dopamine and many other molecules. In addition, after release these neurotransmitters are very quickly metabolized. Although there are significant and important peripheral dopamine receptors, in this way these are not affected by the dopamine released within the brain. Likewise, when one would introduce neurotransmitters, like dopamine, GABA, or others to the peripheral circulation, these agents cannot cross the blood-brain barrier and therfore cannot produce disturbances in the central nervous system (CNS).

Recognizing the importance of various biological membranes and even the cell walls in designing targeted drug delivery is related to the most advanced concepts in improving drug therapeutic index by design.

The very large field which is now considered "site-specific drug delivery" underwent significant development, transformations, and rethinking in the past several years. Various attempts were made to classify all these efforts. One general classification differentiates first-, second-, and third-order targeting[1]. In this, first-order targeting refers to restricted distribution of the drug to the site of action, that is delivery of the drug to specific tissues or an organ. Second-order targeting refers to the selective delivery of the drug to specific host cells, while third-order targeting refers to the directed release of the drug at predetermined intracellular sites. Recent reviews[2-4] describe very well aspects of second- and third-order targeting. Recently, this older classification was used in a renamed form in an extensive review on all kinds of drug delivery systems[5]. Accordingly, site-specific drug delivery systems can be classified as prodrugs, carrier systems, and mechanical pumps. Carrier systems, on the other hand, can further be classified as macromolecular delivery systems, particulate delivery systems, and cellular drug carriers.

A recent comprehensive, excellent review presents a more general approach[6]. The various drug

targeting approaches here are treated based on consideration of the disease and the delivery of the drug in terms of site, access, retention, and timing of interaction, coupled to the duration of the effect of the drug and the responsiveness of the target. This approach is most correct, since it recognizes that too often carriers have been identified without any cognizance of the pathogenesis of the disease. In this way, many times improved site-specific delivery leads to overemphasized claims, although the data suggest that the increase at the selected site of drug concentrations resulted in no or marginal improvement in the treatment of the disease. Of course, this is closely related to the issue presented before, that is, that most currently used drugs were not developed with targeting in mind.

The classification which is most useful to medicinal chemists is mechanism based. According to this classification, the three major classes can be defined as (i) physical, (ii) biological, and (iii) chemical site-specific delivery systems. Accordingly, anything belongs to this class where the targeting is controlled by physical processes, such as local release of pilocarpine from Ocusert (Alza), a polymeric device inserted in the eye, or the particulate delivery systems where the particles containing drugs are localized in the capillaries by virtue of their size, or magnetic interactions.

In the second group, the biological delivery systems, all attempts where the targeting is designed to be performed by bioloigical processes should be included, that is, targeting with monoclonal antibodies, or erythrocyte[7], leucocyte[8], or other cellular drug carriers. A variety of these kinds of carrier systems has already been extensively reviewed in the literature[4-6].

As medicinal chemists, we are concerned primarily with the chemical site-specific delivery systems. Some of these chemical delivery systems have been reviewed before[9,10], and in a more general way more recently[11]. As to how it was defined, in principle, chemical drug delivery systems should include any drug targeting system which requires a chemical reaction to produce it. In other words, there is a covalent link between the drug and the socalled "carrier", and, accordingly, at least one chemical bond needs to be broken for the active component to be released. Within this general definition, "polymeric prodrugs", that is, where polymeric particles or devices chemically bind the drugs, or even antibody-drug conjugates, or derivatized liposomes and albumins, should also be included. However, in the strictest sense, chemical-drug delivery systems (CDS's) refer to *inactive* chemical derivatives of a drug where one or more chemical modifications were done and the newly attached moieties are monomolecular units, generally comparable in size or smaller than the target molecule, and these modifications by design provide a site-specific or site-enhanced delivery of the drug. This in general requires multistep enzymatic and/or chemical transformations[12,13]. The chemical modifications on the drug molecules can be classified into two major groups. The most important group refers to what we call "*targetor moiety*", this is, which is responsible for the targeting, site specificity, lock-in, while the other moieties are introduced to protect certain functions or fine tune the necessary overall molecular properties to achieve the targeting. Here, thus, we introduce the term of "target" moiety, as opposed to "carrier" in order to resolve the various misconceptions about chemical-delivery systems. The targetor (Tor) is a general class, which can include moieties which produce targeting by changing molecular properties of the overall molecule as a result of enzymatic conversions, but also functions which are converted by site-specific enzymes to active functions, etc. In this way, we can clearly differentiate between targetor and carrier, which generally means a function, molecule, or macromolecule which takes or carries the molecule to some desired target. The other moieties or functions introduced into the drug molecule as needed are differentiated from Tor as "protector" functions (F), serving as lipophilizers or protectors of certain parts of the molecule from premature, unwanted metabolic converstion. Thus, we can define a CDS as a drug modified by one Tor and none or as many as needed F functions. And here we can also introduce the difference between

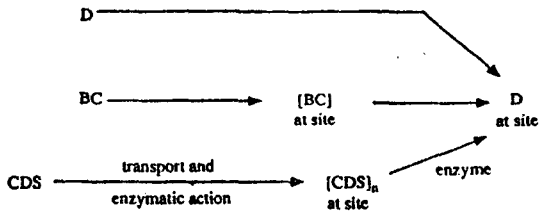

Figure 1—Biological conjugate-BC

prodrugs and the CDS, whereby prodrugs contain one or more F moieties, that is, they are derivatized to produce a protected or enhanced overall delivery form, but they do not contain targetor, Tor functions.

Thus, to summarize, in a physical delivery system, the drug (D) is chemically unmodified, and the physical delivery of the device or the carrier to the site will provide the enhanced concentration of the drug at the active site. The other two approaches ultimately need to deliver a precursor at the site of action.

Fig. 1 shows this classification in a simple diagram. The BC is the biological conjugate which by specific transport is delivered to the site, while the CDS is getting to the site by nonspecific transport combined then with enzymatic reactions providing the concentration of the ultimate $(CDS)_n$ form at the site. In both cases, the BC and the

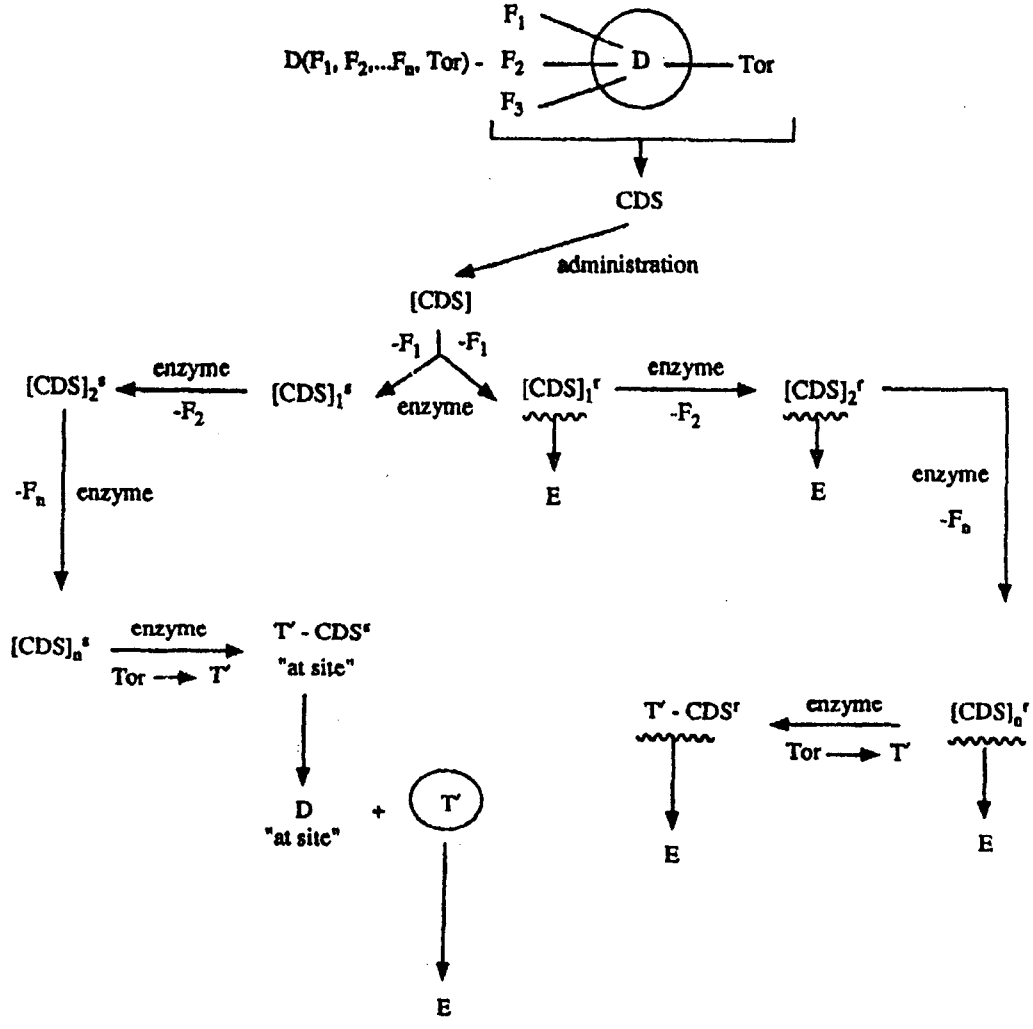

Figure 2—Enzymatic-Physical-Chemical Based CDS

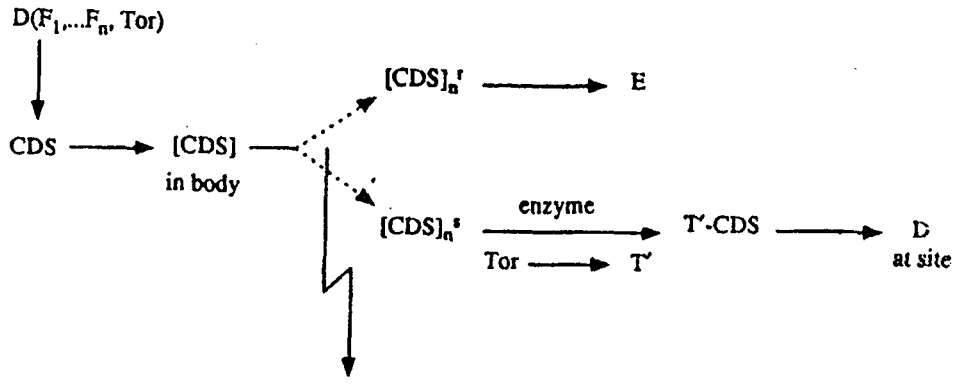

Figure 3—Enzymatic processes

CDS_n are then converted enzymatically to the drug at the site.

Among the various CDS's, we can differentiate three major classes. One is enzymatic-physical-chemical-based targeting; the second is site-specific-enzyme-activated targeting; and the third is receptor-based chemical targeting.

The first, the enzymatic-physical-chemical-based CDS, can be generally described as follows: The drug is chemically modified, introducing the protective functions (F) and the targetor moiety (Tor), resulting in the CDS. Upon administration, the CDS is distributed throughout the body, which arbitrarily is divided as the "site" (^{S}) and the "rest of the body" (^{r}). Predictable enzymatic reactions convert the original CDS by removing some of the protective functions (F) and ultimately modifying the targetor moiety, leading to a still inactive precursor form of the CDS, which is shown here as T'-CDS. This form as well as some of the previous intermediate CDS's are continuously eliminated from "rest of the body". On the other hand, due to the presence of a specific membrane or other distributional barrier, the efflux-influx processes at the site are not the same as the rest of the body. The various modifications and particularly conversion of the targetor to T' will provide a specific concentration of this precursor at the site, ultimately allowing release of the active drug only at the site of action.

The second type of chemical delivery system is what one would call a medicinal chemist's dream. That is, specific enzymes are present only at the site of actions, and these are responsible for converting the chemical delivery system or some alternate chemical delivery system into the active drug. This implies that the specific enzyme is either absent from the rest of the body or for some other reason, such as selective distribution of different rates, does not affect the chemical delivery system or its intermediates elsewhere in the body. This truly site-specific chemical delivery system, when successful, produces a dramatic separation between pharmacologic activity and toxicity. These chemical delivery systems are simplistically described in Fig. 3, according to which, while the CDS can undergo enzymatic transformations throughout the body, the important step of converting the targetor to the active intermediate and subsequently to the active drug is taking place only at the site of action. In other words, the properly designed CDS will be eliminated from the "rest of the body" without producing any activity.

The basic concept behind the physical chemical based drug sequestration is that by strategically modifying the log P of the CDS, in combination with considering the various biological membranes, distributional difference can be achieved. For example, if one considers the blood-brain barrier (BBB) as a biological membrane which is permeable to most lipophilic compounds but does not allow hydrophilic molecules to get across, it is logical to assume that these criteria for transport ap-

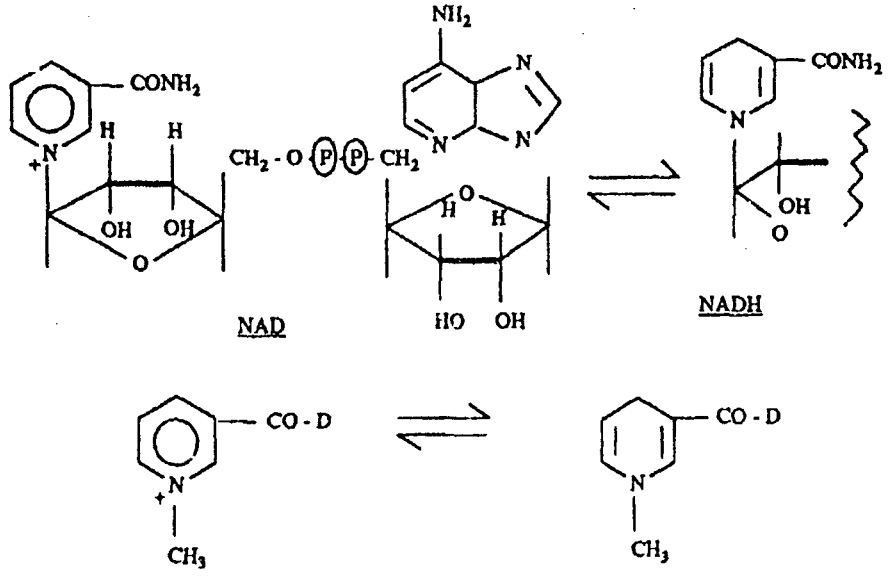

Figure 4—Redox Targetor System

ply in most cases to both sides of the barrier. We have seen the situation when a neurotransmitter synthesized in the brain is not going to reach the blood stream, while introducing in into the blood stream will not result in invasion of the brain; thus, if a lipophilic CDS is converted in the brain to a hydrophilic one, one can assume that it cannot come out; it will be "locked-in". Now it will be too much to ask for this process to take place specifically and exclusively in the brain, but this is not even necessary. Actually, it is advantageous if this conversion from a lipophilic to hydrophilic molecule would take place everywhere in the body. The original lipophilic CDS, after overall distribution, is converted to a hydrophilic one in the whole body, which process will actually accelerate peripheral elimination and will further contribute to brain targeting.

A general system of this kind was developed some years ago[10,14,15], based on the 1-alkyl-dihydronicotinate-quaternary nicotinate system. Accordingly, here the Tor is this redox system where the lipophilic 1, 4-dihydro form is converted *in vivo* to the highly hydrophilic quaternary form. Since this system structurally and from the reactivity point of view is very closely related to the ubiquitous NAD^+-NADH system (Fig. 4), this converstion takes place very easily everywhere in the

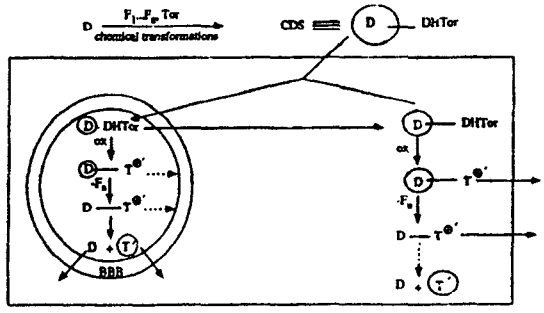

Figure 5

body. The resulting charged T'or-CDS (Ⓓ-$T^{\oplus\prime}$) is locked in the brain, while it is easily eliminated from the body, due to the acquired positive charge. After a relatively short time, the D (in the form of the inactive locked-in D-$T^{\oplus\prime}$) is present in the brain, providing a sustained, brain-specific release of the active drug.

Examples for use of this system for a wide variety of drug classes are abundant. From various steroid homones[16,17], anti-infective agents[17-19], antiviral[20], anticancer agents[21], antiretroviral agents, like AZT, DDI[22-25], and many others have been published. Most recently, successful brain delivery of an enkephalin using a combination of approaches including the redox Tor system was reported [26]. It is important to underline some of the critical

points of the redox Tor system. While the concept is based on the properties of the blood-brain barrier and the differences of its permeability for lipophilic and hydrophilic molecules, toxicity considerations are equally important. The selection of the nontoxic N-methylnicotinate(trigonelline)-dihydrotrigonelline system is critical for the success of this system. Some specific applications of this system will be further reviewed within this symposium[27]. Reviews of many other aspects of this system are also widely available in the literature.

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