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Review

Brain-Targeting Chemical Delivery Systems and Their Cyclodextrin-Based Formulations in Light of the Contributions of Marcus E. Brewster

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ABSTRACT

Here, we present a brief review of brain-targeting chemical delivery systems (CDSs) and their cyclodextrin-based formulations. It is dedicated to the memory of Marcus E. Brewster (1957-2014) and highlights those aspects where he made particularly valuable contributions. During the first two decades of his scientific career that were dedicated to these fields (1978-1997), Marcus was involved in the development of several brain-targeted redox compounds, including design, activity assays, physicochemical characterization, computational modeling of theoretical aspects, and development of cyclodextrin-based formulation for increased stability and water solubility, as well as preclinical and clinical testing. CDSs are designed to provide site-specific or site-enhanced delivery through sequential, multistep enzymatic, and/or chemical transformations. Brain-targeting CDSs incorporate a redox targetor that undergoes enzymatic transformation resulting in a drastic change in physicochemical properties. They can not only increase central nervous system access by making the molecule more lipophilic and enabling its diffusion through the blood-brain barrier, but they can also provide more sustained release by "locking" it behind the blood-brain barrier by subsequently converting it into a hydrophilic intermediate. The origins of the concept (Pro-2-PAM, berberine), one of the most important representative (estradiol-CDS), and the introduction of 2-hydroxypropyl-β-cyclodextrin for improved formulations are discussed in detail.

Introduction

To honor the contributions that Dr. Marcus E. Brewster (October 14, 1957 to September 15, 2014) made to the progress of pharmaceutical sciences as reflected by his about 75 patents and more than 270 publications,[1] here we will review basic aspects of the redox brain-targeting chemical delivery systems (CDSs) and their cyclodextrin (CD)-based formulations, highlighting those parts where Marcus made particularly valuable contributions. He worked on these for more than 2 decades, first as a graduate student and then, after defending his thesis in 1982,[2] as a postdoc at the University of Florida. He continued to work on them as Director of Research at a startup company (Pharmatec) before moving on to become Director of Drug Delivery Research at Janssen Pharmaceutica in 1997. During this time, he was involved in the design and development of several brain-targeted redox compounds, and his contributions covered many areas including design, activity assays, characterization of physicochemical aspects, computational modeling, and development of CD-based formulation for increased stability and water solubility, as well as preclinical and clinical testing. Marcus contributed prolifically to these areas as illustrated by his more than 130 publications on these subjects co-authored with the senior author of this review (N.B.).

Brain-Targeting CDSs: A Multistep Enzymatic Physicochemical Approach

Redox Chemical Delivery Systems

CDSs were developed in the early 1980s to address the challenge of brain-targeted delivery due to the presence of a blood-brain

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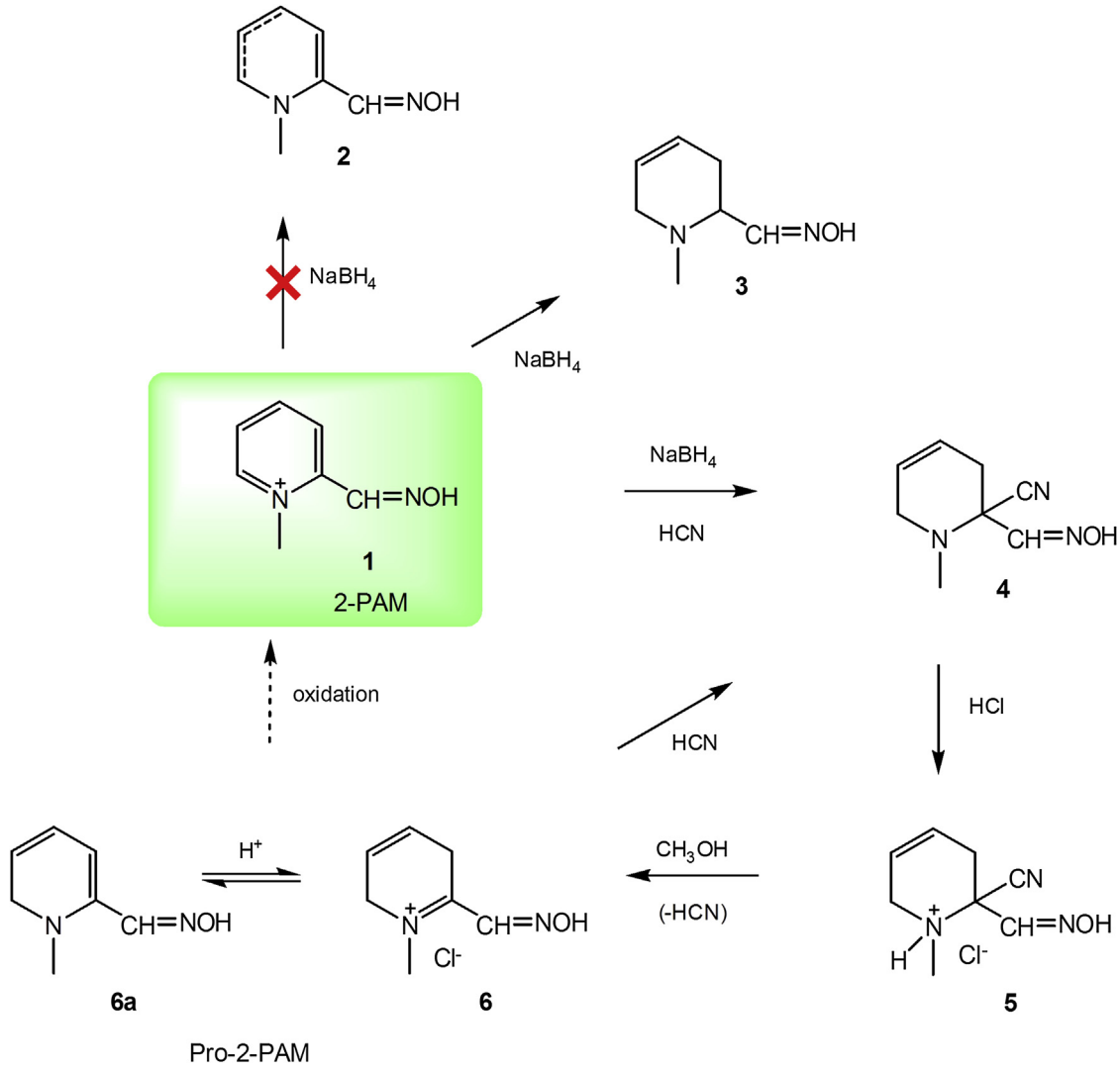

Figure 1. 2-PAM (**1**), an antidote of organophosphate poisoning, could not be transformed into a lipophilic dihydropyridine prodrug such as **2** as the reaction led to the more stable tetrahydro derivative **3**. Pro-2-PAM (**6**) could, however, be easily prepared via **4** and **5**, and it acts as a lipophilic prodrug of 2-PAM that easily crosses the BBB.[17,18]

barrier (BBB)—just when Marcus joined the laboratory of the senior author as a graduate student and published his very first scientific paper on the subject in "Science."[3] The access of xenobiotics to the central nervous system (CNS) is limited because the brain is segregated from the circulating blood by the BBB.[4-6] Brain capillaries lack fenestrations and have tight junctions. Therefore, only lipid soluble compounds can passively cross the BBB, and therapeutic agents that are not lipophilic enough cannot be effectively delivered to the brain. CDSs are inactive chemical derivatives of a drug obtained by one or more chemical modifications designed to provide site-specific or site-enhanced delivery through sequential, multistep enzymatic, and/or chemical transformations. They have been reviewed in detail several times[7-10] including a recent book on retrometabolic drug design that comprises both CDS and soft drug design.[11] Undeniably, the CDS concept evolved from the prodrug concept; however, it became essentially different by the introduction of targetor moieties and by the employment of multistep activation. Although many different strategies have been or are being explored for brain targeting and/or delivery,[12-14] the CDS approach is still the only one attempting not only to increase influx through the BBB, but also to decrease efflux once the compound was delivered. Brain-targeting CDSs exploit the idea that a lipophilic molecule that can cross the BBB and enter the brain, can become "locked in" behind the BBB if it is converted there into a hydrophilic molecule. This is achieved via a specific targetor moiety that undergoes enzymatic transformation resulting in a drastic change of lipophilicity.

Origins of the CDS Concept: Pro-2-PAM

The origins of this CDS concept go back to the mid-1970s and the studies of 2-PAM, a polar quaternary pyridinium, *N*-methyl pyridinium-2-carbaldoxime (2-PAM), **1** (Fig. 1). 2-PAM is the drug of choice to reactivate cholinesterases following organophosphate (OP) poisoning. This is a subject of renewed interest due to increased terrorist activity as OPs are a main ingredient in chemical warfare nerve agents (e.g., sarin) that now also represent a possible terrorist threat. OPs disrupt neurotransmission by rapidly inhibiting acetylcholinesterase (AChE) and prolonging the excitatory action of acetylcholine (ACh) by preventing its hydrolysis and removal from cholinergic receptors. This leads to a buildup of ACh in the nervous system, and results in a variety of signs and symptoms, such as hypersecretion, bronchoconstriction, muscular twitching, mental confusion, convulsive seizures, respiratory