CHEMICAL DELIVERY SYSTEMS:

- The knowledge gained from drug metabolism and prodrug studies may be used to target a drug to its site of action.
- Site-specific chemical delivery requires that the prodrug reaches the target site and that the enzymatic or chemical process exists at the target site for conversion of the prodrug to the active drug.

Many factors are involved in the relative success of site-specific drug delivery, including:

- Extent of target organ perfusion; since high metabolic activity occurs in highly perfused tissues such as liver and kidney, delivery to these organs has a natural advantage.
- Rate of conversion of prodrug to active drug in both target and non target sites; On arrival at the target site, the prodrug should be selectively converted to drug relative to its rate of conversion at non target sites.
- Input/output rates of prodrug and drug from the target sites. It is highly desirable to have the active drug, once formed, migrate from the target site at a slow rate.

Aims of site-specific drug delivery:

- Increased therapeutic effectiveness.
- Limited side effects.

- Other than chemical drug delivery, many carrier systems have been evaluated for drug delivery, including:
- proteins, Polysaccharides, liposomes, emulsions, cellular carriers (erythrocytes and leukocytes), Magnetic control targeting, and implanted mechanical pumps.
- What is the Basic Goal?
  - Protect a non-specific biological environment from a drug
  - Protect a drug from a non-specific biological environment
  - Especially evaluated for drugs with a narrow therapeutic window especially anti-cancer agents

General notes:

- Site-specific drug delivery has been evaluated extensively for drugs with narrow therapeutic windows, such as many of the anticancer drugs.
- The target sites include cancer cells, GI tract, kidney and urinary tract, bacterial cells, viral material, ocular tissue, and the blood—brain barrier.

Examples of site-specific drug delivery:

- The prodrug methenamine can be considered a site-specific chemical delivery system for the urinary tract antiseptic agent formaldehyde. The low pH of the urine promotes the hydrolysis of methenamine to formaldehyde, the active antibacterial agent. The rate of hydrolysis increases with increased acidity (decreased pH), and this can be promoted by administration of urinary pH-lowering agents or by diet. The pH of the plasma is buffered to about 7.4, and the rate of hydrolysis is low, preventing systemic toxicity from formaldehyde.
- The antiviral drugs, such as idoxuridine these drugs serve as substrates for phosphorylating enzymes found in viruses, and the phosphorylated species is the active antiviral agent. The active phosphorylated species is incorporated into viral DNA, disrupting viral replication and, thus, producing the antiviral effect.

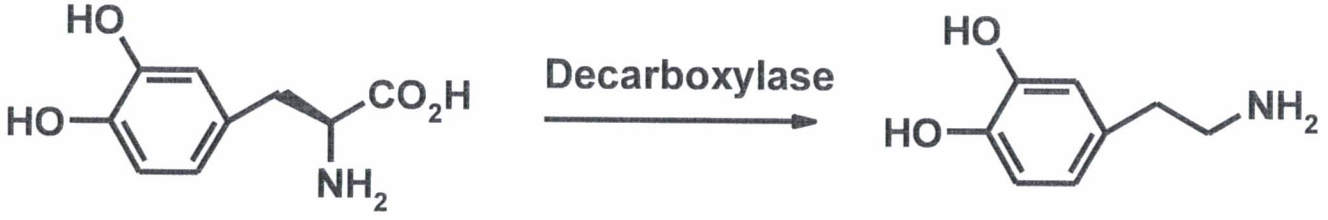
- The relative physicochemical properties of prodrug and its phosphorylated derivative suggest an appropriate input/output ratio for site specificity.
- The reduces any human toxicity that might be associated with this drug is due to:
- A/ phosphorylation is accomplished preferentially by viral thymidine kinase
- B/ increased polarity and viral retention of the active phosphorylated species likely.

The amino acid drug L-dopa

- It can be considered a site specific chemical delivery system that delivers the drug dopamine to the brain.
- The brain has an active transport system that operates to incorporate L amino acids into the central nervous system (CNS), and L-dopa is transported into the brain in this manner.
- Once across the blood—brain barrier, L-dopa undergoes decarboxylation, as shown in the following Scheme to yield the active metabolite, dopamine.

Chemical Delivery Systems

- Example: L-Dopa or Levodopa – Anti-Parkinsonism agent
  - Larodopa® – Roche and Dopar® - Procter & Gamble



Dopamine

- Brain has a specific transport system for L-amino acids

- Dopamine does not cross the blood brain barrier efficiently, is rapidly metabolized by oxidative deamination, and can cause peripheral side effects

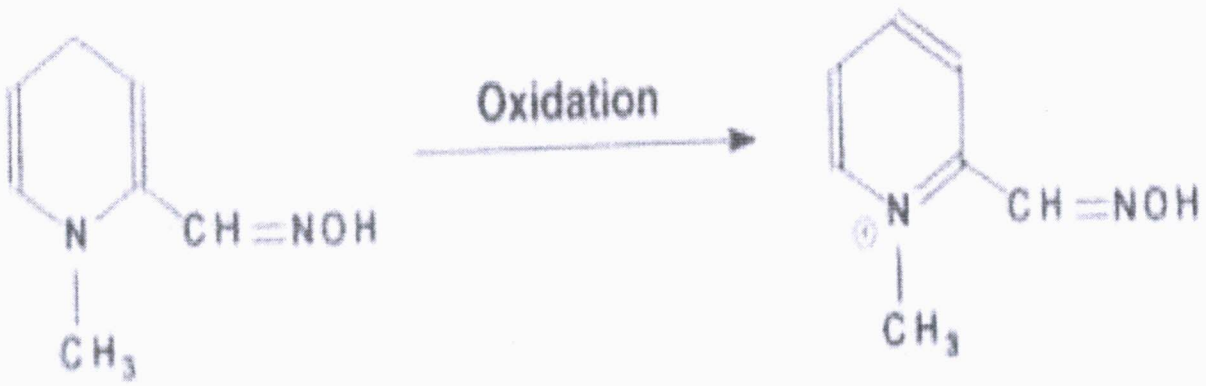
Direct systemic administration of dopamine does not produce significant levels of the drug in the brain because of:

- A/ its high polarity and poor membrane permeability
- B/ its facile metabolic degradation by oxidative deamination.
- Dopamine formed on the inside of the blood—brain barrier is held there, however, because of the poor membrane permeability of this drug.
- Although some specificity for brain tissue is achieved by this delivery method, peripheral side effects of L.-dopa are the direct result of decarboxylation to dopamine in other organ systems.
- In this case, the enzyme activating system is not localized at the target site, and its presence in other tissues and organs leads to undesirable side effects.

(pro-2- PAM)

- Another example of the chemical delivery of a drug to the brain and CNS is the prodrug form of 2-PAM (pro-2- PAM),
- an important antidote for the phosphate and carbamate acetyl cholinesterase inhibitors used in insecticides and nerve gases.
- The polar properties of 2-PAM, a permanent cationic species,
- A/ prevent this drug from being absorbed following oral administration
- B/ restrict the drug from access to the brain, even after IV administration.

- Pro-2-PAM is a dihydropyridine derivative that undergoes metabolic and chemical oxidation to yield the active drug 2-PAM as showing in the following scheme:



Pro-2-PAM

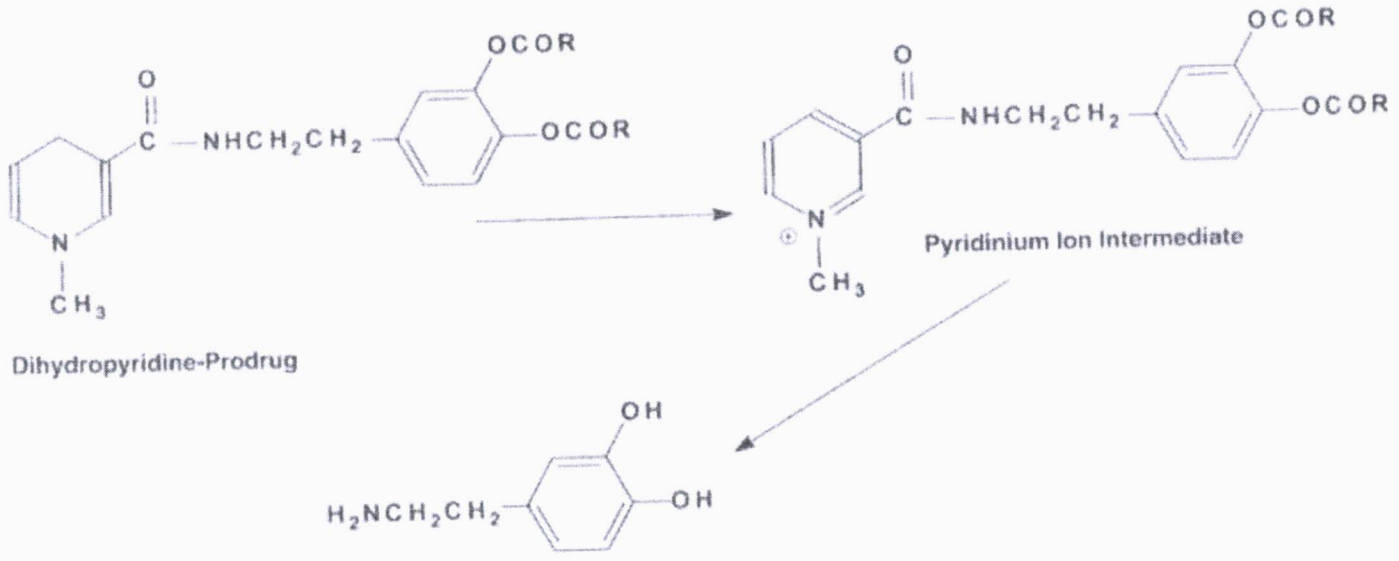
2-PAM

Scheme 5-26 ■ Oxidation of pro-2-PAM.

- The nonionic pro-2-PAM can easily cross the blood—brain barrier, and oxidation to 2-PAM within the brain essentially traps the active cationic drug species inside the brain.
- Oxidation of the dihydropyridine ring of pro-2-PAM occurs throughout the mammalian system, not just in the brain, and the levels of the resulting 2-PAM are approximately the same in peripheral tissue as in the brain.
- Note: IV administration of pro-2-PAM, however, yields brain levels of 2-PAM that are approximately 10 times higher than those achieved by IV administration of the parent drug.

- The facile oxidation of the dihydropyridine ring system has been extensively investigated as a general process for chemical delivery of a number of drugs to the CNS.
- This process is a multistep procedure involving:
- A/ delivery of the drug—dihydropyridine derivative to the brain via facile diffusion across the blood—brain barrier,
- B/ followed by oxidation to the quaternary pyridine cation, which is trapped in the brain.
- C/ the drug is then released from the pyridine cation by a second metabolic/chemical event.

- A number of functional groups can be added to the dihydropyridine to facilitate the derivatization of various functional groups found in CNS drugs.
- Since many CNS drugs are amines, amides of dihydropyridine carboxylic acids are often prepared and used to
- deliver the drugs across the blood—brain barrier into the brain.
- serve to protect the amines from metabolic degradation before they reach the target site.
- The dihydropyridine derivative of a dopamine ester, shown in the following Scheme; has access to the CNS via passive absorption of the tertiary amine, which on oxidation restricts the resulting pyridinium amide to the brain. Amide hydrolysis then delivers the active form of the drug at or near its site of action.

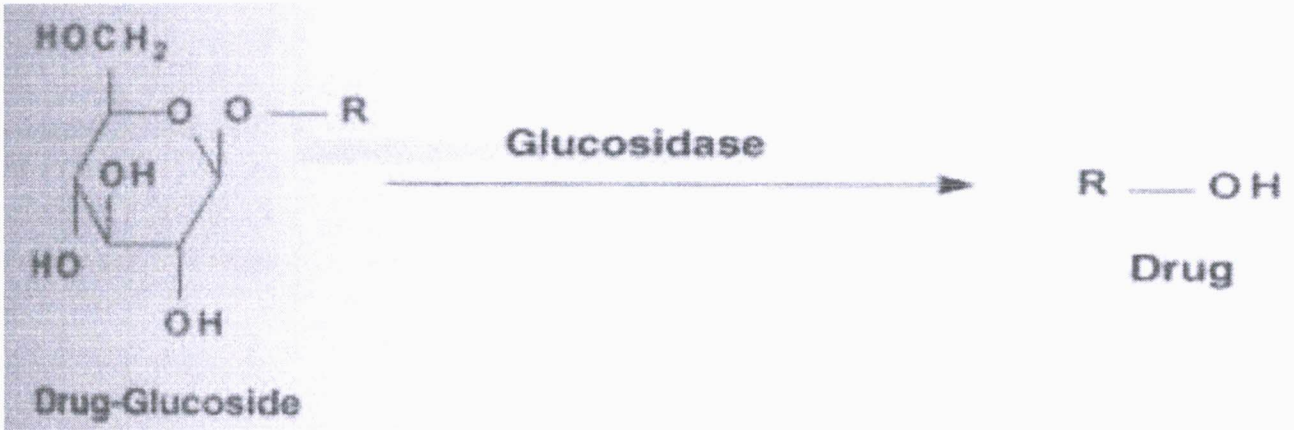


Scheme 5-27 ■ Dihydropyridine-based drug delivery system for dopamine.

- The amide hydrolysis step may be slower than the dihydropyridine oxidation step, and thus a reservoir of pyridinium amide precursor may be available for conversion to the active drug species.

The delivery of drugs to the colon and lower GI tract

- The delivery of drugs to the colon and lower GI tract has taken advantage of the unique enzymatic processes found in colon bacteria. The glucosidase activity of these bacteria allows hydrolysis of glucoside derivatives of drugs in the colon and provides higher concentrations of active drug.
- A number of steroid drugs as shown in the following scheme: demonstrate increased effectiveness in the lower GI tract following administration as their glucoside derivatives.



Scheme 5–28 ■ Activation of drug-glucoside by bacterial glucosidase.

- The polar glucoside derivatives of the steroids are not well absorbed into the bloodstream from the GI tract and remain available to serve as substrates for the bacteria that are found primarily in the human colon.

- Many enzymatic systems show higher activity in tumor cells than in normal tissue because of the higher growth rates associated with tumor tissue.
- Peptidases and proteolytic enzymes are among those systems showing higher activity in and near tumor cells.
- Thus, one means of attempting to produce higher rates of drug incorporation into tumors than in surrounding normal tissue involves deriving a drug molecule with an amino acid or peptide fragment.
- Note: the presence of the enzymes in normal tissue prevents the possibility of complete site specificity for these agents.